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(54) Intermediates in the synthesis of vitamin D derivatives.

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JOURNAL OF ORGANIC CHEMISTRY, vol. 41, no. 12, 11th June 1976, pp. 2098-2102, Washington D.C. (US); D. JOHN ABERHART et al.: "Studies on the adduct of 4-phenyl-1,2,4-triazoline-3,5-dione with Vitamin D3"

CHEMICAL ABSTRACTS, vol. 92, no. 19, 12th May 1980, p. 624, no. 164161d, Columbus, Ohio (US); E.ZBIRAL et al.: "Structural transformations on vitamin D"

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Descripti n

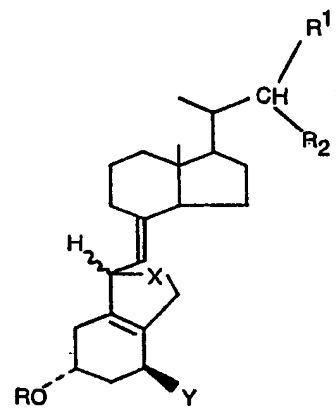
This inventi n relates to novel int rmediates in the production f vitamin D analogu s and of vitamin D analogu s which may be produced therefr m.

In the past modified vitamin D derivatives have been prepared thr ugh m dification f sterol precursors which are then converted into vitamin D derivatives through a standard series of steps, normally preliminary conversions of $\Delta^{5,7}$ dienes followed by irradiation of the dienes to give D vitamins. These procedures have serious flaws. First, all of the available methods for the synthesis of $\Delta^{5,7}$ dienes tend to give mixtures of products or require a number of steps and proceed in relatively low yield. The second difficulty is that the only known transformation of the 5,7 dienes into the vitamins involves irradiation followed by thermal equilibration. Irradiation intrinsically gives rise to a mixture of byproducts. This limits the yield of the desired vitamin and furthermore complicates its recovery in pure form.

Previous attempts to modify the 17-side chain of vitamin D compounds have been unsuccessful due to instability problems. We have now found that vitamin D_2 and related compounds can be converted to a protected form capable of withstanding the reaction conditions necessary for oxidative cleavage of the 22,23-double bond to form a 22-aldehyde which can then be converted to other derivatives as described hereinafter. In particular, we have found that vitamin D_2 compounds in either the *cis* or *trans* configuration can be stabilised by formation of a Diels Alder dienophile adduct which can subsequently be reconverted to the *trans* form of the vitamin after the side-chain modification. The *trans* vitamin analogues can then be efficienctly converted into the active *cis* form by known reactions.

The formation of certain dienophile adducts of vitamin D_3 has been described in the literature. D. J. Aberhart and A. Chi Tung Hsu (J. Org. Chem. Vol. 41, No. 12, 1976, 2098—2102) have described the formation of an adduct with 4-phenyl-1,2,4-triazoline-3,5-dione and E. Zbiral and W. Reischl (Proc. Workshop Vitamin D 1979, 4th. (Vitam. D. Basic Res. Its Clin Appl.), 21—24) have also described the adduct with sulphur dioxide. However, there is no disclosure of the use of these dienophiles to form adducts with vitamin D_2 followed by oxidative cleavage at the 22,23-double bond while leaving double bonds in the 5,10- and 7,8-positions intact.

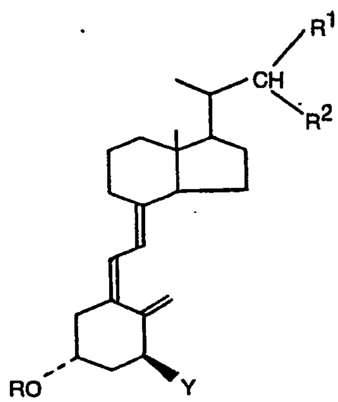
According to one feature of the present invention we provide compounds of the general formula I,



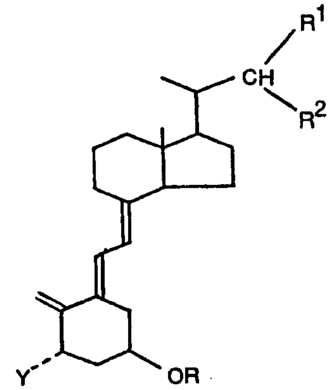
I

wherein R represents a hydrogen atom or a hydroxyl protecting group, Y represents a hydrogen atom or an optionally protected hydroxyl group, X represents —SO_2 or the residue of a diacylazo dienophile and either R^1 represents a halogen atom a hydrocarbylsulphonyloxy group or a group of the formula —Z—R^3 (in which Z represents —O—, —S—, —SO—, —NR^4— or —CR^4R^5— and R^3, R^4 and R^5, which may be the same or different, each represents a hydrogen atom or a straight or branched aliphatic group having 1—12 carbon atoms and which may optionally carry one or more substituents) and R^2 represents a hydrogen atom or R^1 and R^2 together represent an oxo group or an optionally substituted alkylidene group, except that R^1 together with the group —$CH(CH_3)CH$ to which they are attached do not represent a group having the branched 17β-hydrocarbyl side chain skeleton of vitamin D_2 or vitamin D_3.

The ab ve compounds ar useful intermediates in the preparati n of vitamin D analogu s i. . compounds of general f rmulae IV and IVa



IVa (cis)



IV (trans)

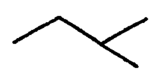
wherein R, Y, R^1 and R^2 are as hereinbefore defined. The above compounds of general formulae IV and IVa are also novel and constitute a still further feature of this invention.

The use of the compounds of general formula I in the preparation of the novel compounds of formulae IV and IVa is illustrated in the reaction scheme of the accompanying drawings, R, Y, X, R^1 and R^2 being as defined above. The compounds of formula I—IV may also carry further groupings.

It should be noted that the Diels Alder adduct formed from either the 5,6-*cis*- or the 5,6-*trans*-vitamin starting material exists as a mixture of two possible isomers at the 6-position. However, since the eventual removal of the Diels Alder residue always generates a compound of the 5,6-*trans* configuration, there is no need to distinguish between such 6-isomers or to effect their separation.

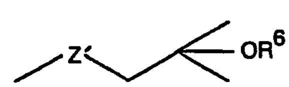
We have found that using the above procedure a wide range of groups R^1 may be introduced into the vitamin D structure. Thus, as indicated above R^1 may be a group of the formula Z—R^3, where Z is —O—, —S—, —SO—, —NR^4 or —CR^4R^5— and R^3, R^4 and R^5, which may be the same or different, are each a hydrogen atom or a straight or branched aliphatic group having 1—12 carbon atoms which may carry one or more substituents such as, for example halogen atoms (e.g. fluorine), or optionally protected hydroxyl groups.

In general it is preferred that the group R^3 in the final products should be of the formula



(in order to provide a 17β-side chain of approximately the shape present in natural vitamin D compounds) with the possibility of substitution as described above. The heteroatoms Z, where present, do not greatly change the overall shape of the side chain.

In particular, the invention enables compounds of formula IV and IVa to be prepared in which R^1 is of formula



wherein Z' represents —O—, —S—, —NH— or —SO— and R^6 represents a hydrogen atom or a hydroxyl protecting group, the 1α-position optionally carrying a hydroxyl or protected hydroxyl group, these being analogues of the active metabolite 25-hydroxy vitamin D^3.

Protected hydroxyl groups may, for example, b acyl groups .g. alkanoyl groups (preferably having 1—6 carbon atoms), aralkanoyl gr ups (preferably having 7—15 carb n at ms), aroyl groups (preferably having 6—12 carbon atoms), cyclic ether gr ups or tri-hydrocarbylsilyl gr ups. Examples f such groups include acetyl, propionyl, benzoyl and tetrahydropyranyl groups and trihydrocarbylsilyl gr ups having up t three C_{1-6} alkyl, C_{6-12} aryl and/ r C_{7-15} aralkyl gr ups.

Th new synthetic analogues of the invention hav modified vitamin D pr p rties of interest in medicine.

The compounds of f rmula IV and IVa in which R^1 has the above m anings may b prepar d, *inter alia*, by nucle philic substitution reacti ns on comp unds of f rmula IV and IVa in which R^1 repr sents a halogen atom, such as a chlorine, br min r iodine at m, or a leaving group, for example a hydrocarbylsulphonyloxy group $O—SO_2R^7$ in which R^7 represents, for example, an alkyl group (preferably having 1—6 carbon atoms), an aryl group (preferably having 7—15 carbon atoms). The tosyloxy group is preferred. Alternatively, the above compounds may be prepared from corresponding compounds of formula I and the dienophile group X removed subsequently. Since, however, the nucleophilic substitution reactions are mostly carried out in the presence of a base and since the protected compounds of formula I are less stable to base than the parent trienes of formula IV and IVa, the latter are commonly preferred substrates.

In the formation of 22-thia compounds (in which Z is —S—), the nucleophilic reagent is conveniently the thiol of formula R^3XX reacted in an inert solvent such as tetrahydrofuran in the presence of a non-nucleophilic base, for example an inorganic base such as sodium hydride or an organic base such as pyridine.

The corresponding sulphoxides (Z= —SO—) may be prepared by oxidation of the thia-compound (Z= —S—), for example using a peracid or salt as oxidising agent, e.g. a periodate. Mixtures of the (R) and (S) sulphoxides are normally formed and the invention extends to these separately and in admixture.

The 22-oxa compounds of formula IV or IVa may be prepared by reaction of an alcohol of formula I, IV or IVa in which R^1 is OH, with an alkylating agent or alternatively by reaction of a reactive derivative thereof, with an alcoholate; these reactions are followed by deprotection when a compound of formula I is used. The reactive derivative may, for example, be a halide such as an iodide, or a hydrocarbylsulphonyloxy derivative, such as a tosyloxy derivative, the alcoholate being, for example, an alkali metal or thallium alcoholate of the alcohol R^3OH. It is preferred, however, to react the compound of formula I, IV or IVa in which R^1 in which R^1 is OH with an epoxide. This generates a side chain carrying a hydroxyl group derived from the epoxide oxygen. Where it is desired to make 25-hydroxy-22-oxa vitamin D_3 derivatives, a suitable reagent is isobutylene epoxide.

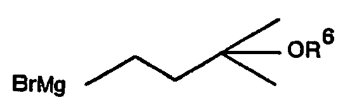
The reaction is advantageously effected in an inert solvent, e.g. a hydrocarbon solvent such as benzene, in the presence of a non-nucleophilic base, conveniently an alkali metal t-alkoxide in the presence of a phase transfer agent such as a crown ether. Under such basic conditions, we have found it especially preferred to effect the reaction on a starting compound of formula IV or IVa, since the trienes are, as indicated above, more stable to these conditions than the dienophile-protected compounds of formula I.

The 22-aza compounds of formula I, IV or IVa may be prepared by reaction of a reactive derivative of an alcohol of formula I, IV or IVa in which R^1 is OH, for example a halide such as an iodide, or a hydrocarbylsulphonyloxy derivative such as a tosyloxy derivative, with an amine of formula R^3R^4NH. Due to the basicity of the reagent, a substrate of formula IV or IVa is preferred. Where the amine is liquid it is preferably reacted without added solvent.

The 22-aza derivatives may often conveniently be isolated as N-acylates, such as N-acetates, which may be formed by reaction with an appropriate acid anhydride.

The 22-hydrocarbylsulphonyloxy derivatives of formulae I, IV and IVa used in the above reactions may be prepared by reacting the corresponding alcohol with the appropriate hydrocarbylsulphonyl halide, e.g. tosyl chloride in the presence of a base such as pyridine. Best results have been obtained by effecting this reaction on a compound of formula I in which X is SO_2, and removing the SO_2 residue by thermolysis, as described hereinafter.

The compounds of formula I, IV or IVa in which Z in R^1 is CR^4R^5 may be prepared by reacting compounds of formula I, IV or IVa carrying a hydrocarbylsulphonyloxy group R^1, e.g. a tosyl group, with carbon nucleophiles. Suitable carbon nucleophiles are Grignard reagents reacted in the presence of a copper catalyst, e.g. a cuprous salt. Thus, for example, 25-hydroxy vitamin D_3 and the 1α-hydroxy derivative thereof may be prepared by reacting an appropriate hydrocarbylsulphonyloxy derivative of formula I, IV or IVa with a Grignard reagent of the formula



(where R^6 has the above meaning) in tetrahydrofuran in the presence of cuprous iodide.

For the production of an alcohol of formula I in which R^1 is OH, for use in the preparation of the above novel vitamin D derivatives, the formyl group in the corresponding aldehyde of formula I (wherein R^1 and R^2 together represent oxo) must be reduced.

We have f und that this can be ffected readily, often in ssentially quantitative yield, by reaction with a metal hydride reducing agent such as an alkali metal b rohydride, .g. s dium b rohydride. It is n t w rthy that this reducti n retains the original configuration at the 20-carb n at m. Such alc hols are als new c mpounds.

Compounds of f rmula I, IV or IVa may also be prepared in which R^1 is a divalent alkyliden group, which may carry substitu nts as described above for R^3. Thus, for xample, the aldehyde of formula I (wherein R^1 and R^2 t gether r present x) may be reacted with an ylid , f r example a Wittig reag nt which may be represented by the g neral formula

$$(R^8)_3P = R^{1A}$$

wherein the groups R^8, which may be the same or different, are alkyl (preferably C_{1-6}), aralkyl (preferably C_{7-15}) or aryl (preferably C_{6-12}) groups and R^{1A} is an alkylidene group (preferably having 1 to 8 carbon atoms) and may carry substituents as described for R^3 above.

The Wittig reagent will normally be formed *in situ* by reaction of a quaternary salt thereof with a strong base in an inert solvent. Suitable bases include hydrocarbyl lithium compounds such as phenyl lithium and *n*-butyl lithium. Suitable solvents include ether solvents such as tetrahydropyran and diethyl ether. The aldehyde of formula I is preferably added immediately after the Wittig reagent has been formed.

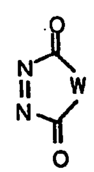
The phosphonium salt precursor of the appropriate Wittig reagent for formation of the correct 17β-side chain of 25-hydroxy vitamin D_3 may, for example be prepared by reaction of isobutylene epoxide with methylenetriphenylphosphorane; the initially formed product in which R^5 is H may if desired be protected, for example by formation of a tetrahydropyranyl or trihydrocarbylsilyl derivative. The phosphorane is preferably prepared by reaction of methyltriphenylphosphonium bromide in a cyclic ether solvent such as tetrahydrofuran in the presence of a strong base such as phenyl or *n*-butyl lithium, the isobutylene epoxide then being reacted *in situ* with a second equivalent of base. We have found the phosphonium bromide initially produced to be difficult to isolate and purify but that conversion to a tetraphenylborate salt enabled a relatively pure product to be obtained.

If it is desired to form a saturated side-chain, selective reduction of the newly formed 22,23-double bond is required. This was unexpectedly found to be possible using hydrogenation over 5% palladium on charcoal. It is noteworthy that this reduction restores the desired, "natural" configuration at the 22- and 23-carbon atoms. This route thus provides a further method of preparing compounds of formula I, IV or IVa in which R^1 is —$CR^3R^4R^5$, as defined above.

It will be seen that the compounds of formula I in the above reaction scheme are key intermediates in the production of the new vitamin D analogues according to the invention. By way of illustration their preparation is now described in detail starting from vitamin D_2 or its 5,6-trans isomer.

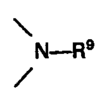
The compound of formula III may be prepared by reaction of a vitamin D_2 compound of formula IIa or IIb with SO_2 or a diacylazo dienophile whereby the desired divalent grouping X is introduced.

Preferred diacylazo dienophiles are cyclic azo compounds such as phthalazine diones or triazoline diones; in general these may be represented by the formula V,



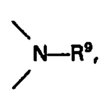
(V)

where W is a divalent aromatic carbocyclic group such as a 1,2-phenylene group or a group



where R^9 is an aryl group such as a phenyl group. The divalent aromatic group or the aryl group R^9 may carry substituents, for example C_{1-6} alkyl or alkoxy groups, halogen atoms or nitro groups. Derivatives of formula III in which X is of formula V are also new compounds.

Where the dienophile is SO_2, this may simply be reacted with the vitamin D_2 compound in a suitable solvent, for example aqueous media capable of dissolving the vitamin. A well stirred mixture of water and a hydrocarbon solvent such as benzene is particularly useful. Basic conditions are preferably used, e.g. using an inorganic base such as an alkali metal bicarbonate. Where the dienophile is a cyclic azo compound of formula V in which W is a group



this may be added to the starting vitamin D_2 c mpound in solution in a suitable s lvent such as ethyl acetat . Where W is a divalent-1,2-arylene grouping as in phthalazin 1,2-dion , h wever, this is pr ferably formed *in situ* by oxidation of the corresp nding cyclic hydrazid , e.g. phthalhydrazid . Thus the vitamin D_2

comp und may be r acted in solution in an inert s lv nt such as a halogenated hydr carbon with th cyclic hydrazid in the pr sence of an oxidising agent such as l ad tetraac tat /acetic acid.

After formati n f th adduct of f rmula III, the 22,23-doubl b nd may be cleaved to form the 22-formyl derivative of formula I by known xidative techniques such as permanganate/peri dat , smate/periodate or, most preferably ozonolysis. We have found that this reaction proceeds selectively in high yield with little cleavage of the 7,8-double bond and, in particular, with no disturbance of the stereochemistry at the 20-position.

Oznolysis may be effected by passing ozone, preferably diluted with a further gas such as oxygen, through a solution of the compound of formula III in a solvent therefor to form an ozonide which is then reductively cleaved by a suitable reducing agent. A suitable solvent is, for example, a halogenated hydrocarbon such as dichloromethane, a ketone, e.g. methyl ethyl ketone or acetone or an alcohol such as methanol or ethanol. A mixture of dichloromethane and methanol gave especially good yields. The reducing agent may be present during the reaction or added after ozonide formation is completed. Thus, for example tetracyanoethylene may be present in solution in acetone during ozonolysis. While reducing agents such as dimethyl sulphide may be used to reduce the ozonide after its formation, preferred reagents are trivalent phosphorus compounds such as triphenylphosphine.

Where an alcohol solvent is used, the aldehyde product of formula I may form an acetal derivative with the alcohol. This may, however, readily be cleaved hydrolytically, for example using an aqueous base e.g. sodium bicarbonate. The reaction is preferably carried out at low temperatures, for example, −78°C.

After modification of the 17-side chain, the residue X may be removed to yield, as indicated above, a 5,6-trans vitamin of general formula IV. The removal of the residue X will be effected in different ways, depending on its nature.

Where X is SO_2, it is conveniently removed by thermolysis under basic conditions, e.g. in the presence of a hydroxylic solvent such as an alcohol, e.g. ethanol, containing a base such as an alkali metal carbonate, e.g. sodium carbonate.

Where X is a group of formula V, removal can readily be effected by removal of the —CO—W—CO— moiety, for example by basic hydrolysis or treatment with hydrazine, followed by mild oxidation of the unsubstituted vitamin hydrazide so formed to the corresponding azo-compound which spontaneously decomposes to yield the required 5,6,-trans vitamin. Basic hydrolysis can be effected using strong alkali such as sodium or potassium hydroxide, for example in solution in an alcohol such as methanol, or by treatment with an amine such as triethylamine. The preferred method, however, is treatment with hydrazine which produces the desired hydrazide in high yield; this reaction has not previously been described for decomposition of such Diels-Alder adducts. Oxidation may be effected using reagents capable of oxidising hydrazo compounds to azo compounds, for example ceric, cupric, ferric, ferricyanic or periodate salts or air. A preferred mild reagent, however, is a diaryl telluroxide such as dianisyl telluroxide, preferably used with a reoxidant such as 1,2-dibromotetrachloroethane and a base such as K_2CO_3 as described in our British Patent Specification No. 2058758A.

Where a 1α-hydroxy vitamin D compound is required, the modified 5,6-trans-vitamin compound of formula IV, which carries the desired 17-side chain, optionally protected, may be subjected to 1α-hydroxylation, using the procedure of our South African patent No. 79/5958. Thus, the 5,6-*trans* vitamin compound may be reacted with a selenite ester, preferably formed *in situ* by reaction of selenium dioxide and an alcohol such as methanol. The quantity of selenium compound may be reduced if a re-oxidant is employed, for example a periodate salt or N-methyl morpholine 1-oxide.

Alternatively, a reactive derivative of a 22-hydroxy derivative of formula I or IV above may be 1α-hydroxylated by the above procedure and the desired side-chain built up subsequently.

The 5,6-*trans* vitamin D compound of formula IV, after modifications such as those described above, may readily be isomerised in high yield to a required active *cis*-vitamin compound by known techniques, for example by irradiation in the presence of iodine or diphenyl selenide or, preferably, a triplet photosensitizer having a triplet energy of the order of 45±5 Kcal per mole, such as anthracene, acridine or phenazine. To avoid isomerization to undesired tachysterol derivatives, acid conditions should be avoided and the photoisomerisation is preferably effected in the presence of a base such as triethylamine.

Where protected hydroxyl groups are present in the vitamin product, these may be removed by conventional methods. In general, the vitamin structure is somewhat sensitive to acids, but is resistant to basic conditions and the latter are advantageously used. Acyloxy groups can thus be removed using alkali metal hydroxide in an alcohol solvent such as methanol. Silyl groups may be removed by treatment with quaternary ammonium fluorides such as tetra-*n*-butylammonium fluoride. Since most of the reactions described above can be applied to compounds having unprotected hydroxyl groups, protecting groups may be removed, if desired, at various stages. Although the vitamins are resistant to bases (and sensitive to acids), the dienophile adducts tend to be sensitive to bases and relatively resistant to acids. Consequently, acid conditions may be used to deprotect hydroxyl groups at stages where the dienophile residue X is present.

In g neral, most f th stages describ d above proceed in excellent yield. Wh n c nditi ns are ptimised, yields f the rd r f 80% r more at each stage hav b n achieved. This renders the verall yield of modified vitamin, starting fr m vitamin D_2, markedly better than those achieved using many previously suggest d r ut s.

The following Examples are given by way of illustration only:—

Microanalyses and *mass spectra* were obtained by the staff at the Institut de Chemie des Substances Natur lles du CNRS, Gif-sur-Yvett , France. *Melting points* were determined using either a K fler block, Mel-temp or Fisher-Johns apparatus and ar uncorrected. *Optical rotations* were measured at room temperature using a Rudolph Photoelectric Polarimeter, Model 70, and are reported for chloroform solutions unless otherwise stated. *UV spectra* were recorded using a Carey 11 spectrophotometer and are reported for ethanol solutions. The molar extinction coefficient (ε) for these absorbances are given in parenthesis. *IR spectra* were recorded using a Perkin-Elmer 137 "Infracord" spectrophotometer and are reported for KBr discs unless otherwise stated. Absorbance characteristics are denoted by s = strong, m = medium, w = weak, sh = shoulder, br = broad. ^{1}*Hnmr spectra* were determined at 60MHz on a Varian T-60 spectrometer. NMR characteristics are denoted as s = singlet, d = doublet, tr = triplet, q = quartet, m = multiplet, W = peak width at half height and are reported for $CDCl_3$ solutions, unless otherwise indicated, with tetramethylsilane as internal standard, as values of δ (ppm downfield of TMS).

Thin layer chromatography (tlc) was carried out on 250μ silica gel GHLF "Uniplates" (Analtech, USA); and preparative layer chromatography (plc) on 1 mm silica gel GF-254 "Uniplates" (Analtech, USA). "Chromatography" refers to medium pressure liquid chromatography carried out using E. Merck silica gel 60H. High performance liquid chromatography (HPLC) was carried out using Waters Associates silica gel "Porasil A" packed in two 2 ft × 3/8 inch stainless steel columns, and a Waters Associates chromatograph, equipped with a 6000 psi pump and a differential refractometer detector. Ozone was generated from a Towers Ozone Apparatus GE-150. Selective ozonolysis requires vigorous mixing of the dissolved substrate and the oxygen-ozone gaseous mixture. A "Vibromixer" (Chemapag, Switzerland) equipped with a stainless steel gas inlet/stirrer was particularly useful for this purpose. This equipment was also used for the formation of the phthalazine-1,4-dione Diels-Alder adducts of vitamin D.

A 200W Hanovia medium pressure mercury vapour lamp (654A36) was used as irradiation source fo 5,6-double bond photoisomerisation reactions.

Reactions on calciferol substrates were routinely performed under an inert, argon atmosphere. Calciferols were stored at −20°C, under argon, in the dark, as either crystalline solids or (where possible) ether solutions. Solvents used were reagent grade unless otherwise stated.

Aqueous work-up refers to partition between an organic solvent and water, followed by sequential washing with a 5% aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution. The organic solution was dried using either anhydrous $MgSO_4$ or anhydrous Na_2SO_4, and the solvent removed on a rotary evaporator. Acid work-up refers to partition between an organic solvent and water, followed by sequential washing with a 4% aqueous HCl solution; 5% aqueous sodium bicarbonate solution, etc. as for aqueous work-up.

Example 1

(a) 6(R),19-[4′-phenyl-1′,2′,4′-triazolidine-3′,5′-dione-1′,2′-yl]-9,10-sec-3β-hydroxy-ergosta-5(10),7(E), 22(E)-triene

To ergocalciferol (5 g) in ethylacetate (150 ml) at 0°C under an argon atmosphere, 4-phenyl-1,2,4-triazoline-3,5-dione (2.4 g, 1.1 eq) in ethyl acetate (150 ml) was added over 45 min. After a further 1 hr, some of the title adduct had precipitated. The mixture was filtered and the filtrate passed down a neutral alumina column. Elution with hexane/ethylacetate gave the remainder of the product. Crystallisation from alcohol gave 6.2 g (86%). mp 99°C; $[\alpha]_D = +208°$ (c = 0.76); ^{1}Hnmr δ 7.48 (s, 5H, aryl), 5.22 (m, W=10Hz, C—22H, 23H), 4.98 and 4.73 (an AB system, J=10Hz, C—6H, 7H), 4.2 and 3.85 (an AB system, J=15Hz, C—19H_2), 4.1 (m, C—3H), 0.533 (s, C—18H_3). IR vmax ($CHCl_3$) 3700 (br), 2950 (s), 1775 (m), 1710 (s), 1425 (s)cm^{-1}; mass spec. molecular ion, m/e = 571; (analysis found: % C, 75.63; H, 8.62; N, 7.36; $C_{36}H_{49}O_3N_2$; requires: % C, 75.62; H, 8.64; N, 7.35).

Similarly prepared from ergocalciferol acetate in 85% yield was the corresponding acetate *6(R),19-[4′-phenyl-1′,2′,4′-triazolidine-3′,5′-dione-1′,2′-yl]-9,10-seco-3β-acetoxy-ergosta-5(10), 7(E), 22(E)-triene.*

Crystallised from ethanol.m.p. 85°C; $[\alpha]_D = +183°$ (c = 0.82); ^{1}Hnmr δ 7.48 (s, 5H, aryl), 5.22 (m, W=12Hz, C—3H, 22H, 23H), 4.98 and 4.73 (an AB system, J=10Hz, C—6H, 7H), 4.2 and 3.85 (an AB system J=16Hz, C—19H_2), 2.0 (s, OAc), 0.53 (s, C—18H_3); IR vmax ($CHCl_3$) 2950 (s), 2900 (sh), 1725 (s), 1420 (m)cm^{-1}; mass spec. molecular ion m/e = 613; (analysis found: % C, 74.18; H, 8.11; N, 6.65; $C_{38}H_{51}O_4N_3$; requires: % C, 74.35; H, 8.38; N, 6.85).

(b) Ozonolysis

The adduct from (a) above (250 mg) in acetone (10 ml) containing tetracyanoethylene (55 mg, 1 eq) at −78°C was treated with ozone for 3 min (approx. 1.5 eq). The system was purged with argon whilst warming to room temperature. The product mixture was s parated by plc to give 130 mg of starting material (nmr) and the corresp nding 20(S)-formyl derivative (90 mg, 84%) as a white f am. ^{1}Hnmr δ 9.55 (d, J=3.75Hz, C—22H), 7.45 (s, 5H, aryl), 5.15 (m, W = 12Hz, C—3H), 4.92 and 4.82 (an AB system, J=10Hz, C—6H, 7H), 4.18 and 4.70 (an AB system J=16Hz, C—19H_2), 2.0 (s, OAc), 1.12 (d, J=7H, C—21H_3), 0.57 (s, C—18H_3).

Example 2

(a) R action of ergocalcifer l acetate with phthalazin -1,4-dione

Phthalhydrazid (10 g, 2.5 eq) was suspend d in a solution of erg calciferolacetate (10 g) in dry CH_2Cl_2 (200 ml). The efficiently mix d mixtur was cooled to 0°C, and a s lution of lead tetra-acetate (20 g) in dry CH_2Cl_2 (100 ml) and acetic acid (1 ml) was added dropwise. The reaction was monitored by tlc. Upon completion, the residual phthalhydrazide was filtered off. Aqueous work-up followed by careful crystallisation from ethylacetate gave 7.4 g (54%) of *6(R),19-[N,N-phtalhydrazido]-9,10-seco-3β-acetoxy-ergosta-5(10), 7(E), 22(E)triene.* m.p. 202—203°C; $[\alpha]_D$ = +343° (c = 1.02); UV λmax 238 nm (38250) and 312nm (11300); ^{1}Hnmr δ (8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 5.08 (m, W=10Hz, C—3H, 22H, 23H), 4.78 and 4.22 (an AB system, J=18Hz, C—$19H_2$), 4.75 (d, J=10Hz, C—6H), 2.0 (s, OAc), 0.13 (s, C—$18H_3$); IR vmax (2950 (s), 2900 (sh), 1750 (s), 1660 (s), 1610 (m), 1380 (m), 1355 (m), 1250 (s)cm^{-1}; mass spec. molecular ion m/e = 598; (analysis found: % C, 75.92; H, 8.30; N, 4.61; $C_{38}H_{50}O_4N_2$ requires: % C, 76.22; H, 8.42; N, 4.68). The mother liquors were chromatographed on silica gel to give 3.6 g (26%) of essentially pure *6(S),19-[N,N'-phthalhydrazido]-9,10-seco-3β-acetoxy-ergosta-5(10), 7(E), 22(E)-triene.* Solid from CH_2Cl_2/hexane. m.p. 114—116°C; $[\alpha]_D$ = −306° (c = 0.64); ^{1}Hnmr δ 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 6.0 (d, J=10Hz, C—7H), 5.2 (m, W=10Hz, C—3H, 22H, 23H), 4.83 (d, J=10Hz, C—6H), 4.78 and 4.23 (an AB system, J=18Hz, C—$19H_2$), 2.17 (s, OAc), 0.65 (s, C—$18H_3$); IR vmax 2950 (s), 2900 (sh), 1660 (m), 1380 (m), 1355 (m), 1250 (s)cm^{-1}; mass spec. molecular ion m/e = 598.

(b) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-3β-hydroxy-ergosta-5(10),7(E), 22(E)-triene

To the acetate from (a) above (5 g) in benzene (100 ml) were added NaOH/CH_3OH (1.25 M solution 12 ml). After 20 min, the mixture was diluted with water and CH_2Cl_2. Acid work-up gave an essentially quantitative yield (4.5 g) of the title 3β-hydroxy compound, crystalline from CH_2Cl_2/ether. m.p. 169—171°C; $[\alpha]_D$ = +392°. (c=0.773); ^{1}Hnmr δ 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 5.12 (m, W=9Hz, C—22H, 23H), 4.78 and 4.22 (an AB system, J=18Hz, C—$19H_2$), 4.75 (d, J=10Hz, C—6H), 4.1 (m, C—3H), 0.18 (s, C—$18H_3$). IR v max 3550 (br), 2950 (s), 2900 (sh), 1650 (s), 1610 (m), 1375 (m), 1350 (m)cm^{-1}; mass spec. molecular ion m/e = 556; (analysis found: % C, 77.76; H, 8.78, N, 5.17; $C_{36}H_{48}O_3N_2$ requires: % C, 77.66; H, 8.69; N, 5.03.

(c) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-3β-tetrahydropyranyloxyergosta-5(10), 7(E), 22(E)-triene

The alcohol from (b) above (4.5 g) in benzene (100 ml) was stirred overnight with dihydropyran (10 ml) and p-toluene sulphonic acid (10 mg). Aqueous work-up gave the title THP ether (204c) (5 g, 96%). Crystalline from CH_2Cl_2/ether. m.p. 151—154°C; $[\alpha]_D$ = +332° (c = 1.25); ^{1}Hnmr δ 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W = 10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 5.07 (m, W=9Hz, C—22H, 23H), 4.78 and 4.22 (an AB system, J=18Hz, C—$19H_2$), 4.75 (d, J=10Hz, C—6H), 4.7 (m, THP, C—2'H), 4.02 (m, C—3H), 3.5 (m, W=20Hz, THP, C—$6'H_2$), 0.17 (s, C—$18H_3$); IR v max 2950 (s), 2900 (sh), 1650 (s), 1610 (m), 1370 (s), 1350 (s), 1030 (s)cm^{-1}; mass spec. molecular ion m/e = 640.

(d) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-3β-[t-butyldimethylsilyloxy]ergosta-5(10), 7(E), 22(E)-triene

The alcohol from (b) above (4.5 g) in CH_2Cl_2 (20 ml) was treated with t-butyl-dimethylsilylchloride (1.9 g) and imidazole (2.7 g) at room temperature for 1.5 hr. Addition of water followed by acid work-up and crystallization from CH_2Cl_2/hexane gave 5.1 g (94%) of the silyl ether. m.p. 203—205°C; $[\alpha]_D$ = +313° (c = 1.5); ^{1}Hnmr δ 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 5.08 (m, W=9Hz, C—22H, 23H), 4.78 and 4.22 (an AB system, J=18Hz, C—$19H_2$), 4.75 (d, J=10Hz, C—6H), 4.03 (m, C—3H), 0.88 (s, t-butyl), 0.17 (s, C—$18H_3$), 0.07 (s, Si—CH_3), 0.05 (S, Si—CH_3); IR v max 2950 (s), 2900 (sh), 1650 (s), 1610 (m), 1370 (s), 1350 (s), 1090 (s)cm^{-1}; mass spec. molecular ion m/e = 670; (analysis found: % C, 74.98; H, 9.26; N, 4.13; $C_{42}H_{62}O_3N_2Si$ requires: % C, 75.18; H, 9.31; N, 4.18.

(e) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-3β-methoxyethoxymethoxyergosta-5(10), 7(E), 22(E)-triene

The alcohol from (b) above (4.5 g) in CH_2Cl_2 (100 ml) was stirred overnight at room temperature with methoxyethoxymethylchloride (8 ml) in the presence of diisopropylethylamine (20 ml). Acid work-up followed by chromatography and crystallisation from CH_2Cl_2/hexane gave 4.3 g (83%) of the MEM ether. m.p. 123—125°C; $[\alpha]_D$ = +325° (c = 1.295); ^{1}Hnmr δ 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 5.15 (m, W=9Hz, C—22H, 23H), 4.82 (s, —OCH_2O—), 4.78 and 4.22 (an AB system, J=18Hz, C—$19H_2$), 4.75 (d, J=10Hz, C—6H), 4.0 (m, C—3H), 3.67 (m, W=6Hz, —OCH_2CH_2O—), 3.43 (s, OCH_3), 0.18 (s, C—$18H_3$); IR γ max 2950 (s), 2900 (sh), 1650 (s), 1610 (m), 1470 (m), 1450 (m), 1370 (s), 1340 (s), 1100 (s), cm^{-1}; mass spec. molecular ion m/e = 644; (analysis found: % C, 74.72; H, 8.57; N, 4.13; $C_{40}H_{66}O_5N_2$ requires: % C, 74.50; H, 8.75; N, 4.34.

(f) General procedure for the ozonolysis of the ergostane side chain

The adduct (from (a), (c), (d) or (e) above (4—5 g) in CH_2Cl_2 (130 ml) and methanol (60 ml) was cool d t −78°C. The efficiently mixed soluti n was treated with an zon -oxyg n mixtur (approx. 1 mmol O_3/min) f r 8—12 min (tlc control) and then thor ughly purged with dry argon for approx. 5 min. Triphenylphosphin (2.5—3 g) was added and the mixture, after appr x. 30 min at −78°C (tlc m nit ring f the br akd wn

of the methoxyhydroper xide intermediates) was shaken with 5% aqueous $NaHCO_3$ (to pr vent dimethyl acetal formation) and allowed to warm t ro m temp rature. The lay rs were separated and th rganic soluti n dried. Chr matography thr ugh silica gel (40—50 g) gave th ald hyde (75—86%) free fr m any f the C—20 (R) pimer (nmr). The following compounds were prepared in this manner.

1) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-3β-acetoxy-20(S)-formylpregna-5(10),7(E)-diene

Crystalline from CH_2Cl_2/ether. m.p. 192—193°C; $[\alpha]_D$ = +382°(c = 1.235); ^{1}Hnmr δ 9.55 (d, J=3Hz, C—22H), 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 5.17 (m, C—3H), 4.78 and 4.22 (an AB system, J=18Hz, C—$19H_2$), 4.75 (d, J=10Hz, C—6H), 2.07 (s, OAc), 1.07 (d, J=7Hz, C—$21H_3$), 0.22 (s, C—$18H_3$); IR vmax ($CHCl_3$) 2950 (m), 2900 (sh), 1740 (s), 1645 (s), 1610 (m), 1370 (m), 1350 (m), cm^{-1}; mass spec. molecular ion m/e = 530; (analysis found: % C, 72.13; H, 7.12; N, 5.20; $C_{32}H_{38}O_5N_2$ requires: % C, 72.43; H, 7.22; N, 5.28).

2) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-3β-tetrahydropyranyloxy-20(S)-formyl-pregna-5(10), 7(E)-diene

Crystalline from CH_2Cl_2/ether. m.p. 154—156°C; $[\alpha]_D]$ = +356° (c = 0.84); ^{1}Hnmr δ 9.42 (d, J=3Hz, C—22H), 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 4.78 and 4.22 (an AB system, J=18Hz, C—$19H_2$), 4.75 (d, J=10Hz, C—6H), 4.69 (m, THP, C—2'H), 4.0 (m, C—3H), 3.5 (m, W=18Hz, THP, C—6'H_2), 0.95 (d, J=6Hz, C—$21H_3$), 0.23 (s, C—$18H_3$). IR vmax 2950 (s), 2900 (sh), 1725 (s), 1640 (s), 1610 (m), 1370 (m), 1350 (m), 1025 (s), cm^{-1}; mass spec. molecular ion m/e = 572; (analysis found: % C, 72.89; H, 7.58; N, 4.78; $C_{35}H_{44}O_5N_2$ requires: % C, 73.40; H, 7.74; N, 4.89).

3) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-3β-[t-butyldimethylsilyloxy]-20(S)-formyl-pregna-5(10), 7(E)-diene

Crystalline from CH_2Cl_2/hexane. m.p. 195—197°C; $[\alpha]_D$ = +335° (c = 1.64); ^{1}Hnmr δ 9.52 (d, J=3Hz, C—22H), 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 4.78 and 4.22 (an AB system, J=18Hz, C—$19H_2$), 4.75 (d, J=10Hz, C—6H), 4.07 (m, C—3H), 1.07 (d, J=7Hz, C—$21H_3$), 0.88 (s, t-butyl), 0.22 (s, C—$18H_3$), 0.07 (s, Si—CH_3), 0.03 (s, Si—CH_3); IR vmax 2950 (s), 2900 (sh), 1740 (s), 1650 (s), 1610 (s), 1350 (s), 1090 (s), cm^{-1}; mass spec. molecular ion m/e = 602; (analysis found: % C, 71.57; H, 8.49; N, 4.51; $C_{36}H_{50}O_4N_2Si$ requires: % C, 71.72; H, 8.36; N, 4.65).

4) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-20(S)-formyl-3β-methoxyethoxymethoxy-pregna-5(10), 7(E)-diene

Crystalline from CH_2Cl_2/hexane, m.p. 136—137°C; $[\alpha]_D$ = +327° (c = 0.62); ^{1}Hnmr δ 9.49 (d, J=3Hz, C—22H), 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 4.87 (s, —OCH_2O—), 4.78 and 4.22 (an AB system, J=18Hz, C—$19H_2$), 4.75 (d, J=10Hz, C—6H), 4.03 (m, C—3H), 3.7 (m, W=6Hz, —OCH_2CH_2O—), 3.47 (s, OCH_3), 1.07 (d, J=7Hz, C—$21H_3$), 0.22 (s, C—$18H_3$); IR vmax 2950 (m), 2900 (sh), 1740 (m), 1650 (s), 1610 (m), 1370 (m), 1350 (m), 1030 (m).

Example 3

General procedure for the reduction of the C—20(S)-formyl to the C—20(S)-(hydroxyethyl) derivative

The aldehyde compound (2.5—3.5 g) in benzene (60—90 ml) was added dropwise over a 15—20 min period to $NaBH_4$ (0.8—1.0 g) in ethanol (20—30 ml). After the addition, the excess reducing agent was carefully quenched with dilute aqueous HCl. The mixture was diluted with CH_2Cl_2. Aqueous work-up gave the desired alchohol in essentially quantitative yield. The following compounds have been prepared in this manner.

1) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-3β-acetoxy-20(S)-[hydroxymethyl]-pregna-5(10), 7(E)-diene

Crystalline from CH_2Cl_2/ether. m.p. 238—240°C; $[\alpha]_D$ = +363° (c = 0.875); ^{1}Hnmr δ 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 5.07 (m, C—3H), 4.78 and 4.21 (an AB system, J=18Hz, C—$19H_2$); 4.75 (d, J=10Hz, C—6H), 3.47 (m, W=14Hz, C—$22H_2$), 2.05 (s, OAc), 1.0 (broad singlet, C—$21H_3$), 0.17 (s, C—$18H_3$); IR vmax ($CHCl_3$) 3200 (br), 2950 (m), 2900 (sh), 1750 (m), 1650 (s), 1610 (m), 1380 (m), 1350 (m), cm^{-1}; mass spec. molecular ion m/e = 532.

2) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-20(S)-[hydroxymethyl]3β-tetrahydropyranyloxy-pregna-5(10), 7(E)-diene

Crystalline from CH_2Cl_2/ether, m.p. 170—173°C; $[\alpha]_D$ = +341° (c = 0.58); ^{1}Hnmr δ 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 4.78 and 4.22 (an AB system, J=18Hz, C—$19H_2$), 4.75 (d, J=10Hz, C—6H), 4.67 (m, THP, C—2'H), 4.0 (m, C—3H), 3.5 (m, W=18Hz, C—$22H_2$, THP, C—6'H_2), 1.0 (broad singlet, C—$21H_3$), 0.19 (s, C—$18H_3$); IR vmax 3600 (br), 2950 (s), 2900 (sh), 1650 (s), 1610 (m), 1370 (m), 1350 (m), 1025 (m), cm^{-1}; mass spec. molecular ion m/e = 574; (analysis found: % C 72.96; H, 7.96; N, 4.73; $C_{35}H_{46}O_5N_2$ requires: % C, 73.14; H, 8.07; N, 4.87).

3) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-3β-[t-butyldimethylsilyloxy]-20(S)-[hydroxymethyl]-pregna-5(10), 7(E)-diene

Crystalline from CH_2Cl_2/hexane. m.p. 145—148°C; $[\alpha]_D$ = +312° (c = 1.22); ^{1}Hnmr δ 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 4.78 and 4.22 (an AB system, J=18Hz, C—$19H_2$),

4.75 (d, J=10Hz, C—6H), 4.03 (m, C—3H), 3.4 (m, W=14Hz, C—22H_2), 1.0 (br ad singlet, C—21H_3), 0.88 (s, t-butyl), 0.19 (s, C—18H_3), 0.07 (s, Ci—$CH_3)_2$); IR vmax 3500 (br), 2950 (s), 2900 (sh), 1640 (s), 1610 (m), 1340 (s), 1250 (s), 1090 (s), cm^{-1}; mass spec. molecular ion m/e = 604; (analysis f und: % C, 71.56; H, 8.70; N, 4.47; $C_{36}H_{52}O_4N_2Si$ requires: % C, 71.48; H, 8.67; N, 4.63).

Example 4

6(R),19-[N,N'-phthalhydrazido]-9,10-seco-3β-acetoxy-20(S)-ethenylpregna-5(10), 7(E)-diene

Methyltriphenylphosphonium bromide (60 mg, 1.2 eq) was suspended in THF (6 ml). n-Butyl lithium (1.5 M solution 0.15 ml) was added. To the resulting orange-coloured solution, the 3β-acetoxy aldehyde from Example 2(f) (1) (100 mg) in benzene (6 ml) was added quickly. After a further 10 min, water was added and the mixture extracted with CH_2Cl_2. Acid work-up followed by purification by plc gave 75 mg (75%) of the title product. Crystalline from CH_2Cl_2/ether. m.p. 173—175°C; $[\alpha]_D$ = +386° (c = 0.86); ^{1}Hnmr δ 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 5.6—4.8 (m, C—3H, 22H, 23H_2), 4.78 and 4.21 (an AB system, J=18Hz, C—19H_2), 4.75 (d, J=10Hz, C—6H), 2.03 (s, OAc), 0.95 (d, J=7Hz, C—21H_3), 0.17 (s, C—18H_3); IR vmax 2950 (m), 1740 (s), 1650 (s), 1610 (m), 1370 (s), 1350 (s), 1260 (s), 1230 (s), cm^{-1}; mass spec. molecular ion m/e = 528; (analysis found: % C, 75.03; H, 7.72; N, 5.21; $C_{33}H_{40}O_4N_2$ requires % C, 74.97; H, 7.63; N, 5.30).

Example 5

(a) Preparation of isobutylene epoxide

To methylallyl chloride (200 ml), 186 g) cooled in an ice bath was added 80% H_2SO_4 (H_2SO_4, 95%, 109 ml; H_2O, 40 ml, 1 eq) over a 30 min period. The temperature of the mixture was maintained between 5—10°C. After a further 3 hr the mixture was added to ice and diluted to a total volume of approx. 100 ml. The layers were separated and the organic residue distilled to remove the by-product β,β-dimethylvinyl chloride and unreacted starting material. These materials are removed below 80°C. The darkly coloured distillation residue is 1-chloro-2-methyl-propan-2-ol (128a) δ 3.47 (s, 2H), 2.97 (s, 1H, exchanges with D_2O), 1.32 (s, 6H). This material was used without further purification.

To a 500 ml round bottom flask containing KOH (200 g) in water (125 ml) at 80°C and fitted with a mechanical stirrer and condenser, was added dropwise the crude chlorohydrin. The crude epoxide distilled directly from the reaction mixture. Redistillation gave isobutylene epoxide (48 g, 35%), b.p. 51°C (lit.[128c] 52°C); ^{1}Hnmr δ 2.6 (s, 2H), 1.33 (s, 6H).

(b) 4-bromo-2-methyl-2-hydroxy-butane

To ethyl-3-bromo-propionate (21 g) in ether (150 ml) at 0°C was added methylmagnesium bromide (3 M soln. in ether, 125 ml, excess) dropwise. After the addition was complete, the mixture was stirred for a further 2 hrs at room temperature. After cooling again to 0°C, the mixture was carefully quenched with NH_4Cl (30 g) in water (200 ml). The layers were separated and the ether layer washed with water until neutral, followed by brine, and dried. Evaporation gave the crude bromo-alcohol (227a) ^{1}Hnmr δ 3.53 (t, J=9Hz, 2H), 2.93 (s, 1H, exchanges with D_2O), 2.07 (t, J=9Hz, 2H), 1.27 (s, 6H); [lit.[171] 3.54 (t, J=8.5Hz, 2H), 2.65 (s, broad, 1H), 2.10 (t, J=8.5Hz, 2H), 1.26 (s, 6H)].

(c) 4-Bromo-2-methyl-2(triethylsilyloxy)-butane

Half of the crude bromide from (b) above in ether (50 ml) containing pyridine (5 ml), imidazole (10 g) and triethylsilylchloride (10 ml) was stirred for 2 days at room temperature. Water was added. Acid-work-up followed by chromatography gave 11 g (62% from the propionate) of the desired compound, homogeneous by tlc. ^{1}Hnmr δ 3.52 (m, 2H), 2.03 (m, 2H), 1.25 (s, 6H), 1.2—0.2 (m, 15H); IR vmax (thin film) 3000 (s), 2950 (sh), 1460 (m), 1420 (m), 1380 (m), 1365 (m), 1230 (s), 1195 (s), 1170 (m), 1100 (s), 1040 (s), 1010 (s), 965 (m), 840 (w), 740 (s), 720 (s), cm^{-1}.

(d) 3-Methyl-2-buten-1-yl-triphenylphosphonium bromide

The bromide from (c) above (1 g) and triphenylphosphine (0.9 g) in benzene (4 ml) was thoroughly degassed, and then heated to reflux. After 3 days, the insoluble material was filtered off to give 1.2 g (85%) of phosphonium salt (228). Recrystallised from CH_2Cl_2/ETOAc. m.p. 234—238°C (lit.[119b] 236—239°C); ^{1}Hnmr δ 8.17—7.67 (m, 15H, aryl), 5.18 (m, W=18Hz), 4.73—4.2 (m, 2H), 1.67 (d, J=5Hz, 3H), 1.31 :d, J=5Hz, 3H); IR vmax 2900 (w), 1590 (w), 1490 (m), 1435 (s), 1110 (s), cm^{-1}.

(e) Methyldiphenylphosphine oxide

Methyltriphenylphosphonium bromide (6 g) was refluxed overnight with KOH (5 g) in water (70 ml). The mixture was allowed to cool to room temperature and then extracted (3x) with CH_2Cl_2. The organic layer was washed with brin , dried and the solvent removed to give the crude solid product (3.5 g) in essentially quantitative yield. Recrystallised fr m acetone. m.p. 113—114°C (lit.[132] 109—111°C); ^{1}Hnmr δ 8.0—7.3 (m, 10H, aryl), 2.03 (d, J=13Hz, 3H); IR vmax 1440 (s), 1175 (s), cm^{-1}; mass spec. molecular i n m/e = 216.

(f) 3-Hydr xy-3-methylbut-1-yl-diphenylph sphine xide

Methyldiphenylphosphine oxide (1.5 g) was suspended in ether (20 ml) at 0°C. BuLi (1.2 eq) was sl wly added, and an orange coloured s luti n formed. To this was added isobutylen epoxide (0.8 ml, 1.3 eq). After approx. 15 min, the mixture was carefully quench d with wat r. This mixture was extracted with CH_2Cl_2 (2x) and the organic layer was washed with 4% aqueous HCl/brine and concentrated. The resulting yellow, oily product was dissolved in a water-ether mixture and the layers separated. The ether layer was washed once with water, and the combined aqueous fractions extracted with CH_2Cl_2 (3x). The organic layer was washed with brine and dried. The solvent was removed and the resulting colourless oil was taken up in benzene and refluxed through a soxhlet containing CaH_2 for 2 hr. The solvent was removed to give crude title compound (1.4 g, 70%; as an oil. ^{1}Hnmr δ 8.0—7.3 (m, 10H, aryl), 2.5 (m, W=34Hz, 2H), 1.83 (m, W=32Hz, 3H), 1.23 (s, 6H); IR vmax (CCl_4) 3500 (m), 2950 (m), 1440 (s), cm^{-1}.

(g) 3-tetrahydropyranyloxy-3-methylbut-1-yl-diphenylphosphine oxide

The phosphine oxide from (f) above (1.4 g) was dissolved in dihydropyran (20 ml) and benzene (5 ml). p-Toluenesulphonic acid (10 mg) was added. After 20 hr, the mixture was concentrated, added to CH_2Cl_2 and washed with 5% aqueous $NaHCO_3$/brine and dried. Evaporation of the solvent gave the crude product (1.8 g) essentially quantitatively as a solid. Recrystallised from acetone. m.p. 146—148°C; ^{1}Hnmr δ 8.0—7.3 (m, 10H, aryl), 4.67 (m, w=6Hz, THP, C—2'H), 3.67 (m, W=36Hz, THP, C—6'H_2), 1.23 (s, 6H); IR vmax 2950 (m), 1440 (m), 118C (s), cm^{-1}; (analysis found: % C, 70.80; H, 7.73; P, 8.54; $C_{22}H_{29}O_3P$ requires % C, 70.96; H, 7.85; P, 8.32.

(h) Preparation of the lithium bromide adduct of the betaine

To methyltriphenylphosphonium bromide (2.898 g) suspended in ether (50 ml) cooled to 0°C was added butyl lithiumn (2.03 M soln.; 4 ml). Isobutylene epoxide (1.0 ml, 1.25 eq) was added and some insoluble material instantly formed. After stirring for 15 min, the reaction mixture was allowed to settle and the supernatant liquid was removed. The resulting solid was suspended in ether and transferred to two centrifuge tubes, and spun. The ether was removed. This process was repeated until the ether washing were colourless (usually 4x). The colourless solid material was dried to give the Li-Br adduct of the betaine (1.5 g) 42%. Beilstein and lithium ion positive, flame tests. IR vmax (nujol) 3500 (br), 3000 (s), 1440 (s), cm^{-1}.

(i) [3-(triethylsilyloxy)-3-methylbut-1-yl]-triphenylphosphonium tetraphenyl borate

To methyltriphenylphosphonium bromide (3 g) suspended in THF (40 ml) was added phenyl lithium (1 eq; 6 ml of a 1.5 M soln.). After 15 min isobutylene epoxide (1 ml, 1.25 eq) was added followed, after a further 5 min, by a second addition of phenyl lithium (1 eq). To this mixture was added benzophenone (1 g; approx. 0.3 eq). After stirring for 20 min, the reaction was quenched with 48% aqueous HBr until just acidic (litmus paper). The organic solvent was removed on a rotary evaporator, water was added and the aqueous layer washed with ether, and the layers separated. The water was removed (rotary evaporator) and the resulting oil taken up in CH_2Cl_2. Aqueous work-up gave the phosphonium salt (226) (3.1 g) 58% as an oil. ^{1}Hnmr δ 8.17—7.67 (m, 15H, aryl), 5.37 (broad s, —OH), 3.8 (m, W=32Hz C—1H_2), 1.8 (m, W=22Hz, C—2H_2), 1.28 (s, (—CH_3)$_2$); IR vmax ($CHCl_3$) 3450 (s), 3000 (s), 1590 (sh), 1440 (s), cm^{-1}.

(j) Silylation

To the phosphonium salt from (i) above (3.7 g) in CH_2Cl_2 (70 ml) was added imidazole (3.4 g) followed by triethylsilylchloride (5 ml). After 40 hr stirring at room temperature, water was added and the mixture diluted with CH_2Cl_2. The CH_2Cl_2 solution after an acid work-up was evaporated and the oily residue partitioned between water and hexane/ether. The water was evaporated and the residue taken up in CH_2Cl_2 which was washed with brine and dried to give on evaporation the salt (226b) (3.6 g, 77%) as an oil.

(k) Anion exchange

To the phosphonium salt from (j) above (3.6 gg) in 95% ethanol (50 ml) was added dropwise, with stirring, a solution of sodium tetraphenyl borate (2.5 g; 1.1 eq) in water (20 ml). An oily residue is formed which solidifies on continued stirring. Filtration gives the phosphonium tetraphenyl borate salt (4.78 g, 92%) as a white, amorphous, non-hygroscopic solid which may be recrystallised from acetone/hexane/ethanol. m.p. 150—151°C; ^{1}Hnmr δ (acetone-d_6) 8.2—6.8 (m, 35H, aryl), 3.53 (m, W=34Hz, C—1H_2), 1.8 (m, W=24Hz, C—2H_2), 1.33 (s, (—CH_3)$_2$), 1.25—0.5 (m, 15H, —SiEt_3); IR vmax 3100 (s), 2950 (s), 1580 (m), 1490 (s), 1440 (s), 1110 (s), 1020 (s), cm^{-1}; (analysis found: % C, 81.41; H, 7.73; P, 3.93; $C_{63}H_{60}BOPSi$ requires: % C, 81.31; H, 7.73; P, 3.96.

(l) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-3β-acetoxy-25-hydroxy-cholesta-5(10),7(E),22(E)-triene

Method A

To methyltriphenylphosphonium bromide (2.898 g) suspended in THF (32 ml) at 0°C was added butyl lithium (2.03 M, 4 ml). Iso-butylen epoxide (720 µl, 1 eq) was sl wly added. After a furth r 15 min, butyl lithium (4 ml) was added. T 3 ml of this s luti n was add d the aldehyde from Exampl 2(f) (1) (300 mg) in benzen (10 ml). The red colour was quickly discharged. Water was add d and the mixture extracted with CH_2Cl_2. After acid work-up th major product was isolated by plc to give the title c mpound (105 mg, 31%).

Method B

Th betain fr m (h) abov (628 mg) was suspended in ther (15 ml) and THF (10 ml). Butyl lithium was added dropwise until a stabl col ur was formed and then a furth r amount (0.75 ml, 2 eq for st r id, 1 eq f r P compound) was added. To this mixture was added th aldehyd from Exampl 2(f) (1)(400 mg) in benzene (6 ml) (approx. 5 min). After the addition, water was added and the mixture extracted with CH_2Cl_2. Work-up as above gave the title compound (155 mg, 34%).

Method C

The phosphonium salt from (h) above (280 mg, 1.5 eq) was dissolved in THF (15 ml) at 0°C. Phenyl lithium (3 eq) was added. The aldehyde (206a) (150 mg, 1 eq) in benzene (6 ml) was added quickly. Tlc showed no change during 30 min and so water was added. Work-up as above, and isolation by plc gave the title product (80 mg, 47%). Crystalline from CH_2Cl_2/ether. m.p. 175—177°C; $[\alpha]_D = +347°$ (c = 0.83); ^{1}Hnmr δ 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 5.27 (m, W=10Hz, C—3H, 22H, 23H), 44.78 and 4.21 (an AB system, J=18Hz, C—19H_2), 4.75 (d, J=10Hz, C—6H), 2.03 (s, OAc), 1.15 (s, C—26H_3, 27H_3), 0.97 (d, J=7Hz, C—21H_3), 0.17 (s, C—18H_3); IR vmax 3800 (m), 2950 (s), 2900 (sh), 1750 (s), 1650 (s), 1610 (m), 1370 (s), 1350 (s), 1240 (s), 965 (m), cm^{-1}; mass spec. molecular ion m/e = 600; (analysis found: % C, 73.94; H, 8.17; N, 4.59; $C_{37}H_{48}O_5N_2$ requires: % C, 73.97; H, 8.05; N, 4.66).

(m) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-3β-acetoxy-25-hydroxy-cholesta-5(10),7(E),22(Z)-triene

To the phosphonium salt from (i) above (1.9 g) in THF (30 ml) was added phenyl lithium (1.5 M soln., 1.7 ml, 1 eq). After a few minutes, the aldehyde (206a) (1 g) in benzene (35 ml) was added dropwise over about 1 min. After a further 3 min, water was added and the mixture diluted with CH_2Cl_2 and given an acid work-up. The reaction was repeated as above and the combined products chromatographed to yield 2.12 g (78%) of a crude, yellow coloured product.

The above mixture (1.4 g) was treated with AcOH:H_2O:THF (8:1:1) (10 ml) for 1.5 hr. Dilution with CH_2Cl_2 followed by aqueous work-up, chromatography and crystallisation gave 1 g of product (85%). Further recrystallisation from CH_2Cl_2/ether, indicated the major component to have the following characteristics. m.p. 182—184°C; $[\alpha]_D = +339°$ (c = 0.84); ^{1}Hnmr δ 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 5.27 (m, W=12Hz, C—3H, 22H, 23H), 4.78 and 4.21 (an AB system, J=18Hz, C—19H_2), 4.75 (d, J=10Hz, C—6H), 2.03 (s, OAc), 1.17 (s,s C—26H_3, 27H_3), 0.9 (d, J=7Hz, C—21H_3), 0.17 (s, C—18H_3); IR vmax 3650 (m), 2950 (s), 2900 (sh), 1750 (s), 1650 (s), 1610 (m), 1370 (s), 1350 (s), 1240 (s), cm^{-1}; mass spec. molecular ion m/e = 600; (analysis found: % C, 74.10; H, 8.15; N, 4.47; $C_{37}H_{48}O_6N_2$ requires: % C, 73.97; H, 8.05; N, 4.66).

(n) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-3β,25-dihydroxy-cholesta-5(10),7(E)-diene

The unsaturated side chain compound from (i) above (450 mg) in benzene (5 ml) and ethanol (5 ml) containing $NaHCO_3$ (100 mg) and 5% Pt/C (150 mg) was stirred under a hydrogen atmosphere for 24 hr. The mixture was filtered through celite and the solvent removed. To the residue, in benzene (10 ml), was added NaOH in methanol (1.25 M soln, 2 ml) and the mixture stirred for 20 min at room temperature. Acid work-up and crystallisation from CH_2Cl_2/ether afforded 380 mg (91%) of the title side chain saturated diol. m.p. 174—177°C; $[\alpha]_D = +408°$ (c = 0.825); ^{1}Hnmr δ 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 4.78 and 4.22 (an AB system, J=18Hz, C—19H_2), 4.75 (d, J=10Hz, C—6H), 4.11 (m, C—3H), 1.22 (s, C—26H_3, 27H_3), 0.87 (broad singlet, C—21H_3), 0.18 (s, C—18H_3); IR vmax 3550 (s), 2950 (s), 2900 (sh), 1650 (s), 1610 (m), 1370 (s), 1350 (s), cm^{-1}; (analysis found: % C, 74.65; H, 8.66; N, 5.06; $C_{35}H_{48}O_4N_2$ requires: % C, 74.96; H, 8.63; N, 5.00).

Example 6

General procedure for the conversion of the phthalazine-1,4-dione adduct to the corresponding 5(E),7(E),10(19)-triene system of the calciferol

The adduct (200—600 mg) was refluxed overnight, under argon in ethanol (10 ml) and hydrazine (3 ml). After cooling to room temperature, the solvents were removed under reduced pressure and the resulting solid taken up in water (30 ml) and CH_2Cl_2 (30 ml). To this two-phase system under argon was added dianisyltellurium oxide (150—450 mg), K_2CO_3 (6 g) and 1,2-dibromotetrachloroethane (3 g), and the mixture stirred for approx. 5 hr (tlc control). After acid work-up the mixture was chromatographed through silica gel (12 g) and the product removed from traces of tellurium oxidant by plc to give the desired vitamin D compound in 85—93% yield.

(1) 9,10-seco-3β,25-dihydroxy-cholesta-5(E),7(E),10(19)-triene

Prepared from the adduct (240b) (200 mg) as described above, to give 131 mg (92%). Solid from ether/hexane. m.p. 79—81°C; $[\alpha]_D = +160°$ (c = 0.735); UV λmax 273 nm (21500); ^{1}Hnmr 6.5 and 5.83 (ABq, J=11Hz, C—6H, 7H), 4.97 (s, C—19H), 4.67 (s, C—19H), 3.85 (m, W=14Hz, C—3H), 1.22 (s, C—26H_3, 27H_3), 0.95 (broad singl t, C—21H_3), 0.55 (s, C—18H_3); IR vmax 3400 (m), 2950 (s), 1620 (w); mass spec. molecular i n m/e = 400; (analysis found % C, 77.50; H, 10.99; $C_{27}H_{44}O_2$ requires: % C, 80.94; H, 11.07; $C_{27}H_{44}O_2 . H_2O$ requir s: % C, 77.46; H, 11.075).

(2) 3β-(3′,5′-dinitrobenzoat) ester

The above crud calciferol (1) (125 mg) in pyridine (5 ml) was treated with 3,5-dinitrobenzoyl chl rid (85 mg, 1.1 eq). Water was added and the mixture diluted with ether. After acid work-up, the ester was isolated by plc (129 mg, 70%). Crystalline from ether/hexane, m.p. 105—107°C: $[\alpha]_D = +168$ (c = 0.97); ^{1}Hnmr δ 9.13 (m, 3H, aryl), 6.62 and 5.82 (ABq, J=11Hz, C—6H, 7H), 5.3 (m, W=14Hz, C—3H), 5.07 (s, C—19H), 4.77 (s, C—19H), 1.23 (s, C—26H_3, 27H_3), 0.93 (broad singlet, C—21H_3), 0.43 (s, C—18H_3); IR vmax 3550 (m), 2950 (s), 2900 (sh), 1750 (s), 1640 (w), 1550 (s), 1350 (s), 1275 (s), cm^{-1}; (analysis found: % C, 68.62; H, 7.85; N, 4.65; $C_{34}H_{46}N_2O_7$ requires: % C, 68.66; H, 7.80; N, 4.71).

Example 7

(a) 9,10-seco-3β,25-dihydroxy-cholesta-5(Z),7(E),10(19)-triene

A solution of the 5,6-*trans* compound from Example 6(1) (126 mg) in benzene (30 ml) containing triethylamine (2 drops) and anthracene (25 mg) was thoroughly degassed. A hanovia lamp (number 654A36) was placed such that the outside of the water cooled jacket was 15 cm from the reaction vessel. The mixture was irradiated for 25 min and the title 5,6-cis compound isolated by plc (93 mg, 74%). Crystalline from acetone/water. m.p. 98—100°C (lit.[174] 95—100°C); $[\alpha]_D = +77°$ (c = 0.26); UV λmax 262 nm (19060); ^{1}Hnmr δ 6.25 and 6.1 (ABq, J=11Hz, C—6H, 7H), 5.05 (s, C—19H), 4.83 (s, C—19H), 3.9 (m, W=18Hz, C—3H), 1.27 (s, C—26H_3, 27H_3), 0.95 (broad singlet, C—21H_3), 0.55 (s, C—18H_3); IR vmax 3500 (s), 2950 (s), 2900 (sh), 1640 (w), 1480 (m), 1380 (m), 1055 (s), cm^{-1}; (analysis: $C_{27}H_{44}O_2 . H_2O$ requires: % C, 77.46; H; 11.08; found: % C, 77.29; H, 11.08). The melting point of an authentic sample supplied by Roussel Uclaf, Inc. (Romainville France) did not depress on mixing.

(b) 3-(3′,5-dinitrobenzoate) ester

Prepared as previously described in Example 6(2). Crystalline from ether/hexane. m.p. 149—150°C (lit.[172] 147—148°C); $[\alpha]_D = +90°$ (c = 0.6); (analysis: $C_{34}H_{46}N_2O_7$ requires: % C, 68.66; H, 7.80; N, 4.71; found: % C, 68.94; H, 7.80; N, 4.52).

Example 8

SO_2 adducts from 9,10-seco-3β-hydroxy-ergosta-5([Z),7(E),10(19),22(E)-tetraene

Sulphur dioxide was slowly passed through a well-stirred mixture of benzene (100 ml) and water (50 ml) containing ergocalciferol (5 g), for a total of 3.5 hr. After this time, air was passed through the mixture for approx. 20 min. Ether and brine were added and the layers separated. Aqueous work-up gave the known sulphur dioxide adducts (172a, 173a) which were used without further purification.

Example 9

(a) 9,10-seco-3β-(triethylsilyloxy)-ergosta-5(E),777(E),10(19),22(E)-tetra-ene

To the 3β-alcohol corresponding to the title compound (4.3 g) in CH_2Cl_2 (50 ml) was added imidazole (4 g) followed by triethylsilylchloride (3 ml). After a few minutes, water was added and the organic layer washed with water/brine and dried. The required silyl ether was isolated essentially quantitatively after chromatography as an oil. UV λmax 274 nm; ^{1}Hnmr δ 6.45 and 5.87 (ABq, J=11Hz, C—6H, 7H), 5.2 (m, W=9Hz, C—22H, 23H), 4.92 (s, C—19H), 4.63 (s, C—19H), 3.82 (m, W=18Hz, C—3H).

(b) 9,10-seco-1α-hydroxy-3β-(triethylsilyloxy)-ergosta-5(E),7(E),10(19),22(E)-tetraene

N-Methylmorpholine N-oxide (NMO) (6.3 g) was stirred with anhydrous $MgSO_4$ in CH_2Cl_2 (50 ml) for 30 min. Selenium dioxide (1.3 g) was stirred in methanol (50 ml) for 45 min and warmed to reflux. The above CH_2Cl_2 mixture was filtered into a solution of the 5,6-*trans*-ergocalciferol derivative from (a) above (5.5 g) in 1,2-dichloroethane (50 ml). This mixture was warmed to reflux and then the hot methanol mixture added, and refluxing of the whole continued for a further 35 min. The heat source was removed and the mixture diluted with CH_2Cl_2. Aqueous work-up followed by chromatography through silica gel (40 g) gave 2.66 g (47%) of the title compound as an oily product. UV λmax 274 nm; ^{1}Hnmr δ 6.57 and 5.90 (ABq, J=11Hz, C—6H, 7H), 5.25 (m, W=9Hz, C—22, 23H), 5.08 (s, C—19H), 4.98 (s, C—19H), 4.65—3.92 (m, C—1H, 3H).

(c) 9,10-seco-1α,3β-dihydroxy-ergosta-5(E(,7(E),10(19),22(E)-tetra-ene

The silylether from (b) above (460 mg) in THF (10 ml) was stirred for 30 min with tetrabutylammonium fluoride (460 mg). The mixture was diluted with CH_2Cl_2 and after aqueous work-up, the title diol was purified by plc to give 305 mg (84%). Crystalline from ether/hexane. m.p. 103—105°C; $[\alpha]_D = +172°$ (c = 0.58); UV λmax 272 nm (22600); ^{1}Hnmr δ 6.38 and 5.82 (ABq, J=11Hz, C—6H, 7H), 5.18 (m, W=9Hz, C—22H, 23H), 4.9 (m, W=9Hz, C—19H_2), 4.53—3.77 (m, C—1H, 3H), 0.57 (s, C—18H_3); IR vmax 3500 (s), 2950 (s), 2900 (sh), 1640 (w), 1460 (m), 1375 (m), 1050 (s), 1030 (s), cm^{-1}; mass spec. molecular ion m/e = 412; (analysis found: % C, 79.57; H, 10.71; $C_{28}H_{44}O_2$ requires: % C, 81.50; H, 10.79; $C_{28}H_{44}O_2 . \frac{1}{2}H_2O$ requires: % C, 79.76; H, 10.76).

(d) 9,10-seco-1α-hydroxy-3β-triethylsilyloxy-ergosta-5(Z),7(E),10(19),22(E)-tetra- n

The 5,6-*trans* c mpound from (b) above (600 mg) in benzene (30 ml) containing phenazine (120 mg) and triethylamine (few dr ps) was phot is merised as above f r 30 min t give 400 mg (66%) of th title

5,6-cis vitamin. UV λmax 263 nm; ^{1}Hnmr δ 6.38 and 6.08 (ABq, J=11Hz, C—6H, 7H), 5.23 (m, W=10Hz, C—19H, 22H, 23H), 5.0 (s, C—19H), '4.6—3.92 (m, C—1H, 3H).

(e) 9,10-s c -1α-3β-dihydroxy-erg sta-5(Z),7(E),10(19),22(E)-tetra-ene

The silyl ether derivative from (d) above (200 mg) was stirred at room temperature in THF (10 ml) with N-Bu_4NF (1 M soln. in THF, 2 ml) for about 30 min. Dilution with CH_2Cl_2 and aqueous work-up followed by purification by plc gave 129 mg (82%). Crystalline from ether/hexane gave the title compound. m.p. 141—143°C (lit.[106] 138—140°C); $[\alpha]_D$ = +34° (c = 0.645); UV λmax 264 nm (19100); ^{1}Hnmr δ 6.35 and 6.05 (ABq, J=11Hz, C—6H, 7H), 5.16 (m, W=14Hz, C—19H, 22H, 23H), 4.98 (s, C—19H), 4.6—3.85 (m, C—1H, 3H), 0.55 (s, C—$18H_3$); IR vmax 3500 (s), 2950 (s), 2900 (sh), 1640 (w), 1460 (m), 1370 (m), 1060 (s), cm^{-1}; mass spec. molecular ion m/e = 412; (analysis: $C_{28}H_{44}O_2$ requires: % C, 81.50; H, 10.75; O, 7.76; found: % C, 81.39; H, 10.60).

Example 10

(a) 9,10-seco-3β-acetoxy-1α-benzoyloxy-ergosta-5(E),7(E),10(19),22(E)-tetra-ene

The 1α-hydroxy-3β-triethylsilyloxy-compound from Example 9(b) (2 g) was treated with benzoyl chloride (2 ml) in pyridine (25 ml). After 30 min water was added and the mixture diluted with ether. After acid work-up, the solvent was removed and the resulting oil stirred overnight in THF:H_2O:AcOH; 8:1:3 (36 ml). After dilution with ether and aqueous work-up, the crude benzoate-alcohol was taken up in benzene (40 ml). Triethylamine (7 ml), acetic anhydride (3 ml) and 4-dimethylaminopyridine (15 mg) were added. After 30 min, water was added and the mixture diluted with ether. Acid work-up and chromatography through silica (10 g) gave 1.76 g (83%) of the title acetate-benzoate as an oil. ^{1}Hnmr δ 8.05 (m, W=12Hz, 2H, aryl), 7.5 (m, W=10Hz, 3H, aryl), 6.58 (d, J=11Hz, C—6H), 5.88 (m, W=16Hz, C—1H, 7H), 5.15 (m, W=10Hz, C—3H, $19H_2$, 22H, 23H), 2.05 (s, OAc), 0.57 (s, C—$18H_3$).

(b) 6(R),19-[N,N'-phthalhydrazido]-9,10-seco-1α-benzoyloxy-3β-acetoxy-ergosta-5(10),7(E),22(E)-triene

To a well-stirred suspension of phthalhydrazide (2 g) in CH_2Cl_2 (200 ml) at 0°C, containing the vitamin from (a) above (2 g), was added dropwise a solution of $Pb(OAc)_4$ (4 g) in CH_2Cl_2 (20 ml) and acetic acid (1 ml). After consumption of starting material (tlc control), the excess phthalhydrazide was removed by filtration. Aqueous work-up and chromatography gave 1.4 g (52% from 248b) of a 95:5 mixture of (250) and the presumed 6(S) isomer. Crystallisation from CH_2Cl_2/hexane gave pure title compound. m.p. 211—213°C; $[\alpha]_D$ = +295° (c = 0.83); ^{1}Hnmr δ 8.5—7.3 (m, 9H, aryl), 5.95 (m, W=14Hz, C—1H, 7H), 5.28 (m, C—3H), 5.17 (m, W=10Hz, C—22H, 23H), 4.92 and 4.37 (an AB system, J=18Hz, C—$19H_2$), 4.8 (m, C—6H), 2.05 (s, OAc), 0.17 (s, C—$18H_3$): IR vmax 2950 (s), 2900 (sh), 1750 (s), 1720 (s), 1640 (s), 1610 (m), 1265 (s), 1245 (s), cm^{-1}; mass spec. molecular ion m/e = 718; (analysis found % C, 75.26; H, 7.54; N, 3.82; $C_{45}H_{54}O_6N_2$; requires: %C 75.18; H, 7.57; N, 3.90).

Example 11

(a) SO_2 adducts of 9,10-seco-3β-(t-butyldimethylsilyloxy)-ergosta-5(E),7(E),10(19),22(E)-tetraene

The crude mixture of sulphur dioxide adducts of ergocalciferol (prepared from 5 g of ergocalciferol as described previously), in CH_2Cl_2 (40 ml), containing imidazole (4 g) was stirred with t-butyldimethylsilyl chloride (3.5 g). After 1.5 hr, the reaction was worked-up as described previously to give, after chromatography, 4.8 g (66%, from ergocalciferol) of the title compound as an oil epimeric at C—6. ^{1}Hnmr δ 5.22 (m, W=9Hz, C—22H, 23H), 4.64 (m, W=10Hz, C—6H, 7H), 4.02 (m, W=16Hz, C—3H), 3.67 (broad s, C—$19H_2$), 0.91 (s, t-Bu), 0.68 + 0.59 (2 × s, C—$18H_3$), 0.07 s, [(Si—CH_3)$_2$].

(b) SO_2 adducts of 9,10-seco-3β-triethylsilyloxyl-ergosta-5(E),7(E),10(19),22(E)-tetra-ene

The crude mixture of sulphur dioxide adducts of ergocalciferol (prepared from 5 g of ergocalciferol as described previously), in CH_2Cl_2 (40 ml), containing imidazole (4 g) was stirred with triethylsilylchloride (3.5 ml). After about 30 min, the reaction was worked up as described previously to give, after chromatography, 5.3 g (74% from ergocalciferol) of (210b) as an oil. ^{1}Hnmr δ 5.22 (m, W=9Hz, C—22H, 23H), 4.64 (m, W=10Hz, C—6H, 7H), 4.02 (m, W=16Hz, C—3H), 3.67 (broad s, C—$19H_2$).

(c) SO_2 adducts of 9,10-seco-3β-(t-butyldimethylsilyloxy)-20(S)-formyl-pregna-5(E),7(E),10(19)-triene

The vitamin D_2 adduct from (b) above (4.7 g) was treated with ozone as described in the general procedure to give, after chromatography, 3.25 g (78%) of the aldehyde (211a). ^{1}Hnmr δ 9.39 (m, C—22H), 4.66 (m, W=16Hz, C—6H, 7H), 4.0 (m, W=16Hz, C—3H), 3.66 (broad s, C—$19H_2$), 1.15 (d, W=6Hz, C—$21H_3$), 0.89 (s, t-Bu), 0.71 + 0.62 (2 × s, C—$18H_3$), 0.05 s, [(Si—CH_3)$_2$]; IR vmax (thin film) 2950 (s), 2900 (sh), 1720 (s), 1660 (w), 1460 (m), 1305 (s), 1250 (s), 1150 (m), cm^{-1}.

(d) Similarly prepared in 82% yield from (b) above was th SO_2 adducts f 9,10-seco-3β-(triethylsilyl xy)-20(S)-formyl-pregna-5(E),7(E),10(19)-trien . ^{1}Hnmr δ 9.57 (m, C—22H), 4.67 (m, W=12Hz, C—6H, 7H), 3.97 (m, W=16Hz, C—3H), 3.65 (broad s, C—$19H_2$), 1.15 (d, J=6Hz, C—$21H_3$); IR vmax (thin film) 2950 (s), 2900 (sh), 1735 (s), 1660 (w), 1460 (m), 1380 (m), 1310 (s), 1150 (m), cm^{-1}.

Example 12

(a) SO_2 adducts f 9,10-seco-3β-(t-butyldimethylsilyloxy)-20(S)-(hydroxymethyl)-pregna-5(E),7(E),10(19)-triene

The ald hyde corresponding to the title compound (3.1 g) was reduced as d scrib d in th general procedure to the title compound in essentially quantitative yield, ^{1}Hnmr δ 4.63 (m, W=12Hz, C—6H, 7H), 4.02 (m, W=16Hz, C—3H), 3.80—3.28 (m, C—19H_2, 22H_2), 1.05 (d, J=6Hz, C—21H_3), 0.87 (s, t-Bu), 0.68 + 0.58 ([2 × s, C—18H_3), 0.05 [s, (Si—CH_3)$_2$]; IR max (thin film) 3550 (br), 2950 (s), 2900 (sh), 1660 (w), 1475 (m), 1350 (s), 1275 (s), 1155 (m), cm^{-1}.

(1) Similarly prepared in greater than 90% yield was the SO_2 adducts of 9,10-seco-3β-(triethylsilyloxy)-20(S)-(hydroxymethyl)-pregna-5(E),7(E),10(19)-triene, ^{1}Hnmr δ 4.63 (m, W=12Hz, C—6H, 7H), 3.93 (m, W=16Hz, C—3H), 3.77—3.17 (m, C—19H_2, 22H_2); IR vmax (thin film) 3550 (br), 2950 (s), 2900 (sh), 1660 (w), 1460 (m), 1380 (m), 1305 (s), 1240 (m), 1155 (m), cm^{-1}.

(2) 9,10-seco-3β-(t-butyldimethylsilyloxy)-20(S)-(hydroxymethyl)-pregna-5(E),7(E),10(19)-triene

Adducts of (1) above (3 g) was stirred in refluxing methanol (50 ml) containing $NaHCO_3$ (3 g) for 2.5 hr. Work-up as described above gave 2.36 g (90%) of the calciferol. UV λmax 274 nm; ^{1}Hnmr δ 6.47 and 5.87 (ABq, J=11Hz, C—6H, 7H), 4.92 (s, C—19H), 4.65 (s, C—19H), 4.1—3.15 (m, C—3H, 22H_2), 1.06 (d, J=5Hz, C—21H_3), 0.9 (s, t-Bu), 0.58 (s, C—18H_3), 0.07 s, [(Si—CH_3)$_2$].

(3) Similarly prepared in 47% yield from the adducts of (1) above after chromatography was 9,10-seco-3β-(triethylsilyloxy)-2;(S)-(hydroxymethyl)-pregna-5(E),7(E),10(19)-triene (267d). UV λmax 273 nm; ^{1}Hnmr δ 6.43 and 5.7 (ABq, J=11Hz, C—6H, 7H), 4.9 (s, C—19H), 4.6 (s, C—19H), 4.03—3.13 (m, C—3H, 22H_2).

Example 13

9,10-seco-3β-hydroxy-20(S)-hydroxymethyl-pregna-5(E),7(E),10(19)-triene

Method A

The phthalazine adduct from Example 3(1) (200 mg) was treated with hydrazine, followed by oxidation as described in the general procedure to give the title product (105 mg; 85%).

Method B

The phthalazine adduct from Example 3(3) (250 mg) was similarly converted to give the *t*-butyldimethylsilyl ether of the title product (166 mg, 90%). This material in refluxing THF (10 ml) was stirred with n-Bu_3NF (1 M soln. in THF, 2 ml) for 1 hr. Dilution with CH_2Cl_2, followed by aqueous work-up and purification by plc gave (267c) (107 mg, 87%).

Method C

The product of Method B (160 mg) obtained via the corresponding SO_2 adducts was siilarly converted to the title compound.

Method D

The triethylsilyl ether of the title compound (160 mg) obtained via the corresponding SO_2 adducts in THF (10 ml) was stirred at room temperature with n-Bu_4NF (1 M soln. in THF, 2 ml). After about 30 min, the reaction was worked up as for (B) above, to give (267c) (101 mg, 85%).

Crystalline from CH_2Cl_2/hexane. m.p. 104—106°C; $[\alpha]_D$ = +190° (C = 0.37); UV λmax 273 nm (22640); ^{1}Hnmr δ 6.5 and 5.83 (ABq, J=11Hz, C—6H, 7H), 4.93 (s, C—19H), 4.62 (s, C—19H), 4.08—3.12 (m, C—3H, 22H_2), 1.05 (d, J=5Hz, C—21H_3), 0.58 (s, C—18H_3); IR vmax 3450 (s), 2980 (s), 2950 (sh), 1635 (w), 1450 (m), 1050 (s), 1030 (s), cm^{-1}; mass spec. molecular ion m/e = 330; (analysis found: % C, 79.46; H, 9.94; $C_{22}H_{34}O_2$ requires % C, 79.95; H, 10.37).

Example 14

6(R),19-[N,N′-phthalhydrazido]-9,10-seco-3β-acetoxy-20(S)-[p-toluenesulphonyloxymethyl]-pregna-5(10),7(E)-diene

The alcohol from Example 3(1) (2.275 g) in pyridine was stirred overnight with p-toluenesulphonylchloride (6.25 g) at room temperature. Water was added to the ice cooled mixture and after about 20 min, the mixture extracted with CH_2Cl_2. Acid work-up followed by crystallisation from CH_2Cl_2/ether gave 2.5 g (85%) of the required tosylate (216). m.p. 91—92°C; $[\alpha]_D$ = +308° (c = 1.26); ^{1}Hnmr δ 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl; and d, J=7Hz, 2H, tosyl), 7.33 (d, J=7Hz, 2H, tosyl), 5.85 (d, J=10Hz, C—7H), 5.06 (m, C—3H), 4.78 and 4.2 (an AB system, J=18Hz, C—19H_2), 4.75 (d, J=10Hz, C—6H), 3.8 (m, W=12Hz, C—22H_2), 2.43 (s, tosyl), 2.03 (s. OAc), 0.88 (d, J=5Hz, C—21H_3), 0.13 (s, C—18H_3); IR vmax 2950 (s), 2900 (sh), 1750 (s), 1650 (s), 1610 (s), 1475 (s), 1240 (s), 1175 (s), cm^{-1}; mass spec. molecular i n m/e = 686; (analysis f und: % C, 68.09; H, 6.844; N, 4.00; S, 4.90; $C_{39}H_{46}O_7N_2S$ requires: % C, 68.19; H, 6.75; N, 4.08; S, 4.67).

Exampl 15

3-methyl-1-butyn-3-yl tetrahydropyranyl ether

3-Methyl-1-butyl-3-ol (25 ml, 21.7 g), dihydropyran (50 ml) and p-toluen sulph nic acid (5 mg) wer mixed t gether at 0°C f r 1 hr, and then stirred at r m temperature f r a furth r 40 hr. The mixtur was concentrated and the residue added to 5% aqueous $NaHCO_3$ and extracted with benzene. The organic solution was dried to give after distillation 37.3 g (86%) of the title ether. b.p. 47°C/0.8 mm Hg (lit. 30—33°C/0.5 mm[50]; 57°C/3.5 mm[170]); ^{1}Hnmr δ 5.6 (m, THP C2'H), 2.45 (s, C—1H), 1.51 (s, CH_3), 1.48 (s, CH_3); IR (thin film) 3350 (s), 2950 (s), 2900 (sh), 1125 (s), 1070 (s), 1030 (s), cm^{-1}.

Example 16

1-mercapto-2-methyl-2-hydroxy-propane

Ethyl-2-mercapto acetate (10 ml) was added to dry ether (150 ml). The well-stirred solution was cooled to 0°C, and an ethereal solution of methyl magnesium bromide (3 M soln., 100 ml., 3.3 eq) was added dropwise over 1.5 hr. The mixture was removed from the ice bath and stirred for an additional 30 min. Ammonium chloride (18 g) in water was carefully added, and the mixture neutralised with hydrochloric acid to form 2 clear layers. The layers were separated and the ether layer washed with water/brine and dried. The solvent was removed under reduced pressure and the product distilled to give 4.4 g of the thiol. b.p. 46°C/16 mm Hg (lit. 64°/26 mm[158a], 61°/22 mm[158b]); ^{1}Hnmr δ 2.6 (d, J=9Hz, C—1H_2), 2.5 (s, exchanges with D_2O, —OH), 1.38 (t, J=9Hz, —SH), 1.28 (s, 6H, —$(CH_3)_2$); mass spec. m/e 59 (100), 73 (24), 91 (14).

Example 17

6(R),19-[N,N'-phthalhydrazido]-23-thia-9,10-seco-3β-acetoxy-25-hydroxy-cholesta-5(10),7(E)-diene

To the tosylate from Example 14 (2.51 g) in THF (125 ml) and HMPTA (3 ml) was added 1-mercapto-2-methylpropan-2-ol from Example 16 (3 ml). The mixture was degassed and NaH (50% dispersion in oil, 1.3 g) was added. After 2 hr, water was added and the mixture diluted with benzene/CH_2Cl_2. Acid work-up followed by chromatography and crystallisation from CH_2Cl_2/ether gave 1.71 g (77%) of the title sulphide. m.p. 187—188°C; $[\alpha]_D$ = +348° (c = 0.62); ^{1}Hnmr δ 8.3 (m, W=12Hz, 2H, aryl), 7.8 (m, W=10Hz, 2H, aryl), 5.9 (d, J=10Hz, C—7H), 5.07 (m, C—3H), 4.78 and 4.18 (an AB system, J=18Hz, C—19H_2), 4.75 (d, J=10Hz, C—6H), 2.58 (s, C—24H_2), 2.03 (s, OAc), 1.23 (s, C—26H_3, 27H_3), 0.98 (d, J=6Hz, C—21H_3), 0.15 (s, C—18H_3); IR νmax 3600 (m), 2950 (s), 2900 (sh), 1740 (s), 1640 (s), 1610 (m), 1370 (s), 1350 (s), 1240 (s), cm^{-1}; mass spec. molecular ion m/e = 620; (analysis found: % C, 69.47; H, 7.63; N, 4.43; S, 5.21; $C_{36}H_{48}O_5N_2S$ requires: % C, 69.64; H, 7.79; N, 4.51; S, 5.17).

Example 18

23-thia-9,10-seco-3β,25-dihydroxy-cholesta-5(E),7(E),10(19)-triene

Prepared from the adduct of Example 17 as described in the general procedure as an oil. UV λmax 273 nm; ^{1}Hnmr δ 6.52 and 5.83 (ABq, J=11Hz, C—6H, 7H), 4.95 (s, C—19H), 4.67 (s, C—19H), 3.85 (m, W=14Hz, C—3H), 2.63 (s, C—24H_2), 1.3 (s, C—26H_3, 27H_3), 1.1 (d, W=6Hz, C—21H_3), 0.58 (s, C—18H_3).

Example 19

3-(3',5'-dinitrobenzoate)-ester

Prepared as described for the compound of Example 6(2) in 67% yield from the adduct of Example 17. Crystalline from ether/hexane. m.p. 108—110°C; $[\alpha]_D$ = +188° (c = 0.742); UV λmax 272 nm (25400) and 262 nm (25400); ^{1}Hnmr δ 9.12 (m, 3H, aryl), 6.62 and 5.82 (ABq, J=11Hz, C—6H, 7H), 5.33 (m, W=12Hz, C—3H), 5.00 (s, C—19H), 4.78 (s, C—19H), 2.63 (s, C—24H_2), 1.27 (s, C—26H_3, 27H_3), 1.08 (d, W=6Hz, C—21H_3), 0.45 (s, C—18H_3); IR νmax 3600 (m), 2950 (s), 2900 (sh), 1740 (s), 1640 (m), 1550 (s), 1350 (s), 1280 (s), 1170 (s), cm^{-1}; mass spec. molecular ion m/e = 612; (analysis found: % C, 64.39; H, 7.26; N, 4.43; S, 5.11; $C_{33}H_{44}O_7N_2S$ requires: % C, 64.68; H, 7.24; N, 4.57; S, 5.23).

Example 20

23-thia-9,10-seco-1α-hydroxy-3β,25-bis(triethylsilyloxy)-cholesta-5(E),7(E),10(19)-triene

To the diol of Example 18 (400 mg) in CH_2Cl (15 ml) was added imidazole followed by triethylsilylchloride (450 μl). After 7 hrs, water was added and the mixture diluted with CH_2Cl_2. Acid work-up gave the crude bis TES derivative which was used without further purification.

Selenium dioxide (106 mg) was stirred in methanol (5 ml) for 45 min. N-methylmorpholine-N-oxide (NMO) (528 mg) was stirred in CH_2Cl_2 (5 ml) in the presence of anhydrous $MgSO_4$ for 30 min. The NMO solution was filtered into a solution of the crude bis TES derivative in 1,2-dichloro ethane (5 ml) and the mixture warmed to reflux. To this refluxing mixture was added the SeO_2/methanol. After 35 min at reflux, the h ating mantl was r moved, the mixture diluted with CH_2Cl_2 and wash d immediately with 5% aque us $NaHCO_3$ and dried. Purification by plc gave 233 mg [35% from the adduct of Example 17 of the title 1α-hydroxy compound as an oil. UV λmax 274 nm; ^{1}Hnmr δ 6.58 and 5.92 (ABq, J=12Hz, C—6H, 7H), 5.08 (s, C—19H), 4.97 (s, C—19H), 4.67—4.03 (m, C—1H, 3H), 2.58 (:s, C—24H_2), 1.32 (s, C—26H_3, 27H_3).

Example 21

23-thia-9,10-sec -1α,3β,25-trihydroxy-cholesta-5(E),7(E),10(19)-triene

To th bis TES derivativ from Example 20 (112 mg) in THF (5 ml), was added anhydrous tetrabutylamm nium fluorid (220 mg) in benzene (3 ml). After 2.25 hr at reflux, the mixtur was dilut d with ethylacetate, washed with water (3×)/brine and dried. The title triol (50 mg, 68%), was isolated by plc. Crystalline from CH_2Cl_2/hexane. m.p. 129—131°C; $[\alpha]_D = +184°$ (c = 0.2175); UV λmax 273 nm (21860); ^{1}Hnmr δ 6.58 and 5.92 (ABq, J=11Hz, C—6H, 7H), 5.12 (s, C—19H), 5.0 (s, C—19H), 4.65—4.0 (m, C—1H, 3H), 2.67 (s, C—$24H_2$), 1.28 (s, C—$26H_3$, $27H_3$), 1.12 (d, J=7Hz, C—$21H_3$), 0.57 (s, C—$18H_3$); IR vmax 3550 (s), 2950 (s), 2900 (sh), 1640 (w), 1050 (m), 1030 (m), cm^{-1}; mass spec. molecular ion m/e = 434; (analysis fund: % C, 71.57; H, 9.57; S, 7.23; $C_{26}H_{42}O_3S$ requires: % C, 71.84; H, 9.74; S, 7.38).

Example 22

23-thia-9,10-seco-3β,25-dihydroxy-cholesta-5(Z),7(E),10(19)-triene

A solution of the 5,6-*trans*-trans vitamin from Example 20 (64 mg) in benzene (30 ml) containing triethylamine (1 drop) and antracene (15 mg) was thoroughly degassed and photoisomerised as described in Example 6(1). The mixture was irradiated for 20 min and the required title vitamin (49 mg, 77%) isolated by plc as an oil. UV λmax 262 nm; ^{1}Hnmr δ 6.25 and 6.0 (ABq, J=11Hz, C—6H, 7H), 5.03 (s, C—19H), 4.82 (s, C—19H), 3.93 (m, W=18Hz, C—3H), 2.67 (s, C—$24H_2$), 1.27 (s, C—$26H_3$, $27H_3$), 1.08 (d, W=6Hz, C—$21H_3$), 0.55 (s, C—$18H_3$).

Example 23

The 3-(3′,5′-dinitrobenzoate ester of the product of Example 22 was prepared using the method of Example 6(2). Crystalline from ether/hexane. m.p. 145—148°C; $[\alpha]_D = +109°$ (C = 0.571); UV λmax shoulders at 260 nm (24900) and 235 nm (30600); ^{1}Hnmr δ 9.08 (m, 3H, aryl), 6.33 and 6.06 (ABq, J=11Hz, C—6H, 7H), 5.33 (m, C—3H), 5.15 (s, C—19H), 4.93 (s, C—19H), 2.65 (s, C—$24H_2$), 1.27 (s, C—$26H_3$, $27H_3$), 1.08 (d, J=6Hz, C—$21H_3$), 0.57 (s, C—$18H_3$). IR vmax 3750 (m), 2950 (s), 2900 (sh), 1750 (s), 1640 (s), 1550 (s), 1345 (s), 1280 (s), 1170 (s), cm^{-1}; mass spec. molecular ion m/e = 612; (analysis found: % C, 64.7; H, 7.24; O, 18.25; N, 4.36; S, 5.15; $C_{33}H_{44}O_7N_2S$ requires: % C, 64.68; H, 7.24; O, 18.28; N, 4.57; S, 5.23).

Example 24

23-thia-9,10-seco-1α-hydroxy-3β,25-bis(triethylsilyloxy)-cholesta-5(Z),7(E),10(19)-triene

The corresponding 5(E) compound of Example 20 (180 mg) in benzene (35 ml) containing phenazine (40 mg) and triethylamine (4 drops) was thoroughly degassed and irradiated as described above for 35 min. 137 mg (75%) of the less polar 5(Z) compound was isolated as an oil by plc. UV λmax 263 nm; ^{1}Hnmr δ 6.35 and 6.05 (ABq, J=11Hz, C—6H, 7H), 5.27 (s, C—19H), 4.95 (s, C—19H), 4.6—3.93 (m, C—1H, 3H), 2.57 (s, C—$24H_2$), 1.2 (s, C—$26H_3$, $27H_3$).

Example 25

23-thia-9,10-seco-1α,3β,25-trihydroxy-cholesta-5(Z),7(E),10(19)-triene

To the corresponding bis TES derivative from Example 24 (185 mg) in THF (8 ml) was added tetrabutylammonium fluoride (1 M soln. in THF, 2 ml). After 1.25 hr at reflux, the mixture was diluted with CH_2Cl_2. Aqueous work-up and purification by plc gave 110 mg (90%) of the title triol. Crystalline from ether/hexane. m.p. 124—126°C; $[\alpha]_D = +54°$ (c = 0.37); UV λmax 264 nm (17400); ^{1}Hnmr δ 6.35 and 6.05 (ABq, J=11Hz, C—6H, 7H), 5.33 (s, C—19H), 5.0 (s, C—19H), 4.65—4.0 (m, C—1H, 3H), 2.63 (s, C—$24H_3$), 1.27 (s, C—$26H_3$, $27H_3$), 1.1 (d, J=6Hz, C—$21H_3$), 0.55 (s, C—$18H_3$); IR vmax 3550 (s), 2950 (s), 2900 (sh), 1640 (w), 1050 (m), 1030 (m), cm^{-1}; mass spec. molecular ion m/e = 434; (analysis found: % C, 71.63; H; 9.61; S, 7.34; $C_{26}H_{42}O_3S$ requires: % C, 71.84; HJ, 9.74; S, 7.38).

Example 26

23-thia-9,10-seco-1α-bis(3′,5′-dinitrobenzoyloxy)-25-hydroxy-cholesta-5(Z),7(E),10(19)-triene

To the triol from Example 25 (75 mg) in pyridine (3 ml) and benzene (5 ml) was added 3,5-dinitrobenzoylchloride (85 mg). Water was added and the mixture diluted with ether. Work-up as in Example 6(2) and purification by plc gave 97 mg (68%) of the unstable bis (dinitrobenzoate). ^{1}Hnmr δ 9.8 (m, 6H, aryl), 6.62 (d, J=11Hz, C—6H), 6.12—5.42 (m, C—1H, 3H, 7H, 19H), 5.32 (s, C—19H), 2.63 (s, C—$24H_2$), 1.27 (s, C—$26H_3$, $27H_3$), 1.08 (broad singlet, C—$21H_3$), 0.22 (s, C—$18H_3$).

Example 27

23-thia-9,10-seco-1α,3β,25-trihydroxy-cholesta-5(Z),7(E),10(19)-triene-23,S-oxides

The sulphide from Example 25 (100 mg) in methanol (10 ml), ether and water (2 ml) was stirred at room temperature with sodium metaperiodate (50 mg). After 3 hr, a further addition of oxidant (20 mg) was made. Aft r a total of 5 hr, the mixture was diluted with CH_2Cl_2. Aqueous work-up followed by plc gave 92 mg (89%) of the titl sulphoxide mixtur . Solid from aceton , methan l/hexane, ether. m.p. 148—155°C; $[\alpha]_D = +77°$ (c = 0.691); UV λmax 263 nm (18150) ^{1}Hnmr δ 6.35 and 6.05 (ABq, J=11Hz, C—6H, 7H), 5.33 (s, C—19H), 5.0 (s, C—19H), 4.62—3.72 (m, C—1H, 3H, —OH, xchanges with D_2O), 2.83 and 2.75 (broad singl ts, C—$24H_2$), 1.52 and 1.38 (C—$26H_3$, $27H_3$), 1.23 (broad singlet, C—$21H_3$), 0.6 (s, C—$18H_3$); IR vmax

3500 (s), 3300 (s), 2950 (s), 2900 (sh), 1620 (w), 1380 (s), 1220 (s), 1070 (s), 1050 (s), 1030 (s), 1600 (s), cm^{-1}; mass spec. molecular i n m/ = 450; (analysis found: % C, 69.05; H, 9.44; S, 7.13; $C_{26}H_{42}O_4S$ requir s: % C, 69.29; H, 9.39; S, 7.12).

Example 28

23-oxa-9,10-seco-3β,25-dihydroxy-cholesta-5(E),7(E),10(19)-triene

The silyl ether from Example 51 (160 mg) was stirred with $n\text{-}Bu_4NF$ (1 M soln. in THF, 1 ml) in refluxing THF (5 ml) for 40 min. Dilution with CH_2Cl_2, followed by aqueous work-up and purification by plc gave the title compound (102 mg, 82%). UV λmax 274 nm; ^{1}Hnmr δ 6.47 and 5.85 (ABq, J=11Hz, C—6H, 7H), 4.9 (s, C—19H), 4.63 (s, C—19H), 3.83 (m, W=18Hz, C—3H), 3.58—3.07 (m, C—$22H_2$), 3.18 (s, C—$24H_2$), 1.2 (s, C—$26H_3$, $27H_3$), 1.03 (d, J=6Hz, C—$21H_3$), 0.58 (s, C—$18H_3$).

Example 29

The 3-(3′-5′-dinitrobenzoate) ester of the product of Example 28 was prepared as described previously for Ex. 6(2). Crystalline from ether/hexane. m.p. 75—77°C; $[\alpha]_D$ = +176° (c = 0.58); ^{1}Hnmr δ 9.15 (m, 3H, aryl), 6.58 and 5.78 (ABq, J=11Hz, C—6H, 7H), 5.3 (m, W=12Hz, C—3H), 5.03 (s, C—19H), 4.73 (s, C—19H), 3.57—3.07 (m, C—$22H_2$), 3.2 (s, C—$24H_2$), 1.22 (s, C—$26H_3$, $27H_3$), 1.02 (d, J=6Hz, C—$21H_3$), 0.47 (s, C—$18H_3$); IR νmax 3500 (m), 2950 (s), 2900 (sh), 1730 (s), 1640 (m), 1550 (s), 1460 (m), 1340 (s), 1270 (s), 1165 (m), cm^{-1}; mass spec. molecular ion m/e = 596; (analysis found: % C, 66.31; H, 7.55; N, 4.56; $C_{33}H_{44}O_8N_2$ requires: % C, 66.42; H, 7.43; N, 4.70).

Example 30

23-oxa-9,10-seco-3β-(t-butyldimethylsilyloxy)-25-hydroxy-cholesta-5(Z),7(E),10(19)-triene

The corresponding 5(E) compound from Example 51 (160 mg) in benzene (30 ml) and triethylamine (3 drops) containing phenazine (35 mg) was thoroughly degassed and irradiated as described above for 30 min. Purification by plc gave (273a) (138 mg, 86%). UV max = 263 nm; ^{1}Hnmr δ 6.25 and 6.0 (ABq, J=11Hz, C—6H, 7H), 5.05 (s, C—19H), 4.82 (s, C—19H), 3.92 (m, W=18Hz, C—3H), 3.62—3.10 (m, C—$22H_2$), 3.20 (s, C—$24H_2$), 1.23 (s, C—$26H_3$, $27H_3$), 1.03 (d, J=6Hz, C—$21H_3$), 0.91 (s, t-Bu), 0.58 (s, C—$18H_3$), 0.05 [s, $(Si—CH_3)_2$].

Example 31

23-oxa-9,10-seco-3β,25-dihydroxy-cholesta-5(Z),7(E),10(19)-triene

The corresponding 3-t-butyldimethylsilyl ether from Example 30 (138 mg) was stirred with $n\text{-}Bu_4NF$ (1 M soln. in THF, 2 ml) in refluxing THF (5 ml). After 45 min, the mixture was diluted with CH_2Cl_2. Aqueous work-up followed by purification by plc gave the diol (273b) (91 mg, 85%) as an oil. UV λmax 263 nm; ^{1}Hnmr δ 6.24 and 6.04 (ABq, J=11Hz, C—6H, 7H), 5.03 (s, C—19H), 4.83 (s, C—19H), 3.92 (m, W=18Hz, C—3H), 3.57—3.12 (m, C—$22H_2$), 3.25 (s, C—$24H_2$), 1.22 (s, C—$26H_3$, $27H_3$), 1.03 (d, J=6Hz, C—$21H_3$), 0.57 (s, C—$18H_3$).

Example 32

The 3-(3′,5′-dinitrobenzoate) ester of the product of Example 31 was prepared as in Example 6(2). Crystalline from ether/hexane m.p. 136—138°C; $[\alpha]_D$ = +101° (c = 0.615); ^{1}Hnmr δ 9.12 (m, 3H, aryl), 6.22 and 6.01 (ABq, J = 11Hz, C—6H, 7H), 5.23 (m, W=18Hz, C—3H), 5.1 (s, C—19H), 4.92 (s, C—19H), 3.57—3.1 (m, C—$22H_2$), 3.2 (s, C—$24H_2$), 1.22 (s, C—$26H_3$, $27H_3$), 1.05 (d, J=6Hz, C—$21H_3$), 0.53 (s, C—$18H_3$); IR νmax 3550 (m), 2950 (s), 2900 (sh), 1750 (s), 1650 (m), 1555.(s), 1470 (m), 1350 (s), 1280 (s), cm^{-1}; mass spec. molecular ion m/e = 596; (analysis found: % C, 66.34; H, 7.37; N, 4.61; $C_{33}H_{44}O_8N_2$ requires: % C, 66.42; H, 7.43; N, 4.70).

Example 33

23-oxa-9,10-seco-3β-(t-butyldimethylsilyloxy)-25-(triethylsilyloxy)-cholesta-5(E),7(E),10(19)-triene

The 25-hydroxy compound from Example 51 (300 mg) in CH_2Cl_2 (10 ml) was treated with triethylsilylchloride (130 µl) in the presence of imidazole (200 mg) for 16 hrs. Acid work-up gave the title bis silylated calciferol (274) which was used in the next step without further purification.

Example 34

23-oxa-9,10-seco-3α-hydroxy-3β-(t-butyldimethylsilyloxy)-25-(triethylsilyloxy)-cholesta-5(E),7(E),10(19)-triene

Selenium dioxide (60 mg) was stirred in methanol (4 ml) for 45 mins. NMO (300 mg) was stirred in CH_2Cl_2 (4 ml) in the presence of anhydrous $MgSO_4$ for 30 min. The NMO solution was filtered into a solution of the bis silyl ether from Example 33 in 1,2-dichloroethane (4 ml) and the mixture warmed to reflux. To this refluxing mixture was added the S O_2/methan l mixtur . After 23 min, th heating mantl was remov d and th product worked up and is lat d as described previ usly t give 190 mg [51% based n Ex. 52] of the titl 1α-hydr xylated product. UV λmax 274 nm; ^{1}Hnmr δ 6.55 and 5.88 (ABq, J=12Hz, C—6H, 7H), 5.1 (s, C—19H), 5.0 (s, C—19H), 4.75—4.02 (m, C—1H, 3H), 3.65—3.12 (m, C—$22H_2$), 3.25 (s, C—$24H_2$).

Example 35

23-oxa-9,10-seco-1α,3β,25-trihydr xy-cholesta-5(E),7(E),10(19)-triene

Th bis silyl ether from Example 34 (190 mg) in THF (6 ml) was refluxed with nBu_4NF (1 M solution in THF, 2 ml) f r 1 hr. The mixtur was diluted with CH_2Cl_2. Aqu us w rk-up gav the titl triol (103 mg, 84%) after purification by plc. Crystalline from chloroform/hexane. mp 141—144°C, $[\alpha]_D = +144°$ (c = 0.355); UV λmax 272 nm (20554); ^{1}Hnmr (400 MHz) δ 6.58 (d, J=12Hz), 5.89 (d, J=12Hz), 5.13 (s, C—19H), 4.98 (s, C—19H), 4.50 (m, W=12Hz, C—1H), 4.26 (m, W=20 Hz, C—3H), 3.43 (m, 1H), 3.30—3.15 (m, C—$22H_2$, $24H_2$), 1.20 (s, C—$26H_3$, $27H_3$), 1.02 (d, J=6Hz, C—$21H_3$), 0.58 (s, C—$18H_3$); IR νmax 3500 (s), 2950 (s), 2900 (sh), 1640 (w), 1450 (m), 1380 (m), 1360 (m), 1045 (s), cm^{-1}; mass spec. molecular ion m/e = 418; (analysis found: % C, 74.76; H, 10.33; $C_{26}H_{42}O_4$ requires: % C, 74.60; H, 10.11).

Example 36

23-oxa-9,10-seco-1α-hydroxy-3β-(t-butyldimethylsilyloxy)-25-(triethylsilyloxy)-cholesta-5(Z),7(E),10(19)-triene

The corresponding 5(E) compound from Example 35 (200 mg) in benzene (35 ml) containing phenazine (40 mg) and triethylamine (4 drops) was irradiated with the hanovia lamp as described previously for 35 min to give, after purification by plc, 155 mg (78%) of the title compound as a less polar, oily product. UV λmax 263 nm; ^{1}Hnmr δ 6.30 and 6.01 (ABq, J=12Hz, C—6H, 7H), 5.23 (s, C—19H), 4.97 (s, C—19H), 4.67—3.9 (m, C—1H, 3H), 3.53—3.07 (m, C—$22H_2$), 3.17 (s, C—$24H_2$).

Example 37

23-oxa-9,10-seco-1α,3β,25-trihydroxy-cholesta-5(Z),7(E),10(19)-triene

The bis silyl ether from Example 36 (155 mg) and $n\text{-}Bu_4NF$ (1 M soln. in THF, 2 ml) were stirred together in refluxing THF (5 ml) for 1 hr. Dilution with CH_2Cl_2 followed by aqueous work-up and purification by plc gave the title triol (252a) (77 mg, 77%). Crystalline from ether/hexane. m.p. 121—123°C; $[\alpha]_D = +47°$ (c = 0.6); UV λmax 264 nm (17200); ^{1}Hnmr δ 6.37 and 6.05 (ABq, J=11Hz, C—6H, 7H), 5.33 (s, C—19H), 5.0 (s, C—19H), 4.57—3.87 (m, C—1H, 3H), 3.6—3.1 (m, C—$22H_2$), 3.23 (s, C—$24H_2$), 1.23 (s, C—$26H_3$, $27H_3$), 1.05 (d, J=6Hz, C—$21H_3$), 0.58 (s, C—$18H_3$); IR νmax 3500 (s), 2950 (s), 2900 (sh), 1640 (w), 1450 (m), 1380 (m), 1360 (m), 1045 (s), cm^{-1}; mass spec. molecular ion m/e = 418; (analysis found: % C, 74.47; H, 9.97; $C_{26}H_{42}O_4$ requires: % C, 74.60; H, 10.11).

Example 38

9,10-seco-3β-(triethylsilyloxy)-20(S)-(p-toluenesulphonyloxymethyl)-pregna-5(E),7(E),10(19)-triene

Method A

To the hydroxy compound from Example 13(D) (400 mg) in pyridine (5 ml) was added tosylchloride (350 mg) and the mixture stirred overnight at room temperature. Water was added and the mixture diluted with ether. Acid work-up gave, after purification by plc, 310 mg (58%) of the title tosylate.

^{1}Hnmr δ 7.73 (d, J=8Hz, 2H, aryl), 7.28 (d, J=8Hz, 2H, aryl), 6.43 and 5.81 (ABq, J=11Hz, C—6H, 7H), 4.92 (s, C—19H), 4.63 (s, C—19H), 4.2—3.57 (m, C—3H, $22H_2$), 2.48 (s, aryl-CH_3); IR νmax (thin film) 2960 (s), 2900 (sh), 1600 (w), 1460 (m), 1360 (s), 1190 (s), 1175 (s), 1090 (s), cm^{-1}.

Method B

The crude SO_2 adducts of 9,10-seco-3β-triethylsilyloxy-20(S)-(hydroxymethyl)-pregna-5(E),7(E),10(19)-triene from Example 12(1) (3.2 g) was stirred overnight in pyridine (40 ml) at 5°C with p-toluenesulphonyl chloride (4 g). The mixture was cooled to 0°C, water added and, after a few minutes, the mixture was diluted with Et_2O. After an acid work-up, the crude oily product (281) was taken up in ethanol (100 ml) and refluxed in the presence of $NaHCO_3$ (4 g) for 1 hr. The mixture was concentrated and partitioned between CH_2Cl_2/water/brine. The organic solution was dried and chromatographed to give 2.64 g (70%) of the required vitamin (278c) nmr and IR identical to the product obtained by Method A.

Example 39

9,10-seco-3β-hydroxy-20(S)-[fluoromethyl]-pregna-5(E),7(E),10(19)-triene

The tosylate from Example 38 (200 mg) in THF (5 ml) was refluxed for 45 min in the presence of $n\text{-}Bu_4NF$ (1 M soln. in THF, 1 ml). The mixture was diluted with CH_2Cl_2. Aqueous work-up followed by purification by plc gave 70 mg (63%) of the title fluoride (279). ^{1}Hnmr δ 6.5 and 5.83 (ABq, J=11Hz, C—6H, 7H), 4.97 (s, C—19H), 4.7 (br, s, C—19H, 22H), 4.2—3.6 (m, C—3H, 22H), 1.1 (d, J=6Hz, C $21H_3$), 0.6 (s, C—$18H_3$).

Example 40

9,10-seco-1α-hydroxy-3β-(triethylsilyloxy)-20(S)-(p-toluenesulphonyloxymethyl)-pregna-5(E),7(E),10(19)-triene

Selenium dioxide (56 mg) was stirred in acetonitrile (3.5 ml) for 45 min. NMO (280 mg) was stirred in CH_2Cl_2 (3.5 ml) in the pres nce of anhydr us $MgSO_4$ f r 30 min. Th NMO soluti n was filtered int a s lution of the 1-des xy compound from Example 387 (308 mg) in 1,2-dichl ro thane (3.5 ml) and th mixture warmed t reflux. T this was added the SeO_2/CH_3CN mixture, and refluxing c ntinued for a further

5.5 min. The reaction mixtur was cooled in an ice bath, dilut d with CH_2Cl_2 and worked up as pr viously to give 180 mg (57%) of the title 1-hydroxy compound. ^{1}Hnmr δ 7.73 (d, J=8Hz, 2H, aryl), 7.28 (d, J=8Hz, 2H, aryl), 6.43 and 5.81 (ABq, J=11Hz, C—6H, 7H), 5.03 (s, C—19H), 4.93 (s, C—19H), 4.63—3.6 (m, C—1H, 3H, $22H_2$), 2.48 (s, aryl-CH_3).

Example 41

9,10-seco-1α,3β-dihydroxy-20(S)-(p-toluenesulphonyloxymethyl)-pregna-5(E),7(E),10(19)-triene

The 3-triethylsilylether derivative from Example 40 (180 mg) in THF (5 ml) containing n-Bu_4NF (1 M soln. in THF, 0.4 ml) was stirred for 15 min. The mixture was diluted with CH_2Cl_2. An aqueous work-up and purification by plc gave 118 mg (81%) of the title diol. Solid from CH_2Cl_2/hexane. m.p. 97—99°C; $[\alpha]_D = +132°$ (c = 0.57); UV λmax 272 nm (23360) and 218 nm (15920); ^{1}Hnmr δ 7.73 (d, J=8Hz, 2H, aryl), 7.28 (d, J=8Hz, 2H, aryl), 6.43 and 5.81 (ABq, J=11Hz, C—6H, 7H), 5.03 (s, C—19H), 4.93 (s, C—19H), 4.63—3.53 (m, C—1H, 3H, $22H_2$), 2.5 (s, aryl-CH_3), 1.02 (d, J=6Hz, C—$21H_3$), 0.57 (s, C—$18H_3$); IR vmax 3500 (s), 2950 (s), 2900 (sh), 1600 (w), 1450 (m), 1355 (s), 1190 (s), 1175 (s), cm^{-1}.

Example 42

9,10-seco-1α-hydroxy-3β-(triethylsilyoxy)-20(S)-(p-toluenesulphonyloxymethyl)-pregna-5(Z),7(E),10(19)-triene

The corresponding 5(E) compound from Example 40 (225 mg) in benzene (35 ml) containing triethylamine (3 drops) was irradiated as described above with anthracene (45 mg) as triplet sensitizer for 30 min to give, after plc, 185 mg (82%) of the title compound. UV λmax 263 nm and 216 nm; ^{1}Hnmr δ 7.73 (d, J=8Hz, 2H, aryl), 7.3 (d, J=8Hz, 2H, aryl), 6.28 and 5.98 (ABq, J=11Hz, C—6H, 7H), 5.28 (s, C—19H), 4.92 (s, C—19H), 4.55—3.58 (m, C—1H, 3H, $22H_2$), 2.45 (s, aryl-CH_3).

Example 43

9,10-seco-1α,3β-dihydroxy-20(S)-(p-toluenesulphonyloxymethyl)-pregna-5(Z),7(E),10(19)-triene

The silyl ether from Example 43 (185 mg) in THF (5 ml) containing n-Bu_4NF (1 M soln. in THF, 0.32 ml) was stirred for 15 min at room temperature. Dilution with CH_2Cl_2 aqueous work-up and purification by plc gave the title diol (110 mg, 73%). UV λmax 263 nm (17427) and 216 nm (18672); ^{1}Hnmr δ 7.68 (d, J=8Hz, 2H, aryl), 7.23 (d, J=8Hz, 2H, aryl), 6.28 and 5.97 (ABq, J=11Hz, C—6H, 7H), 5.27 (s, C—19H), 4.93 (s, C—19H), 4.57—3.6 (m, C—1H, 3H, $22H_2$), 2.45 (s, aryl-CH_3), 1.05 (d, J=6Hz, C—$21H_3$), 0.52 (s, C—$18H_3$).

Example 44

1-amino-2-methyl-2-hydroxy-propane

To a well-stirred mixture of lithium aluminium hydride (12 g) in ether (200 ml) at 0°C was added dropwise over 1 hr a solution of acetone cyanohydrin (11.2 g, 12 ml) in ether (50 ml). The mixture was stirred at room temperature overnight. After cooling to 0°C, water (24 ml) was cautiously added dropwise. After the quenching was complete, anhydrous Na_2SO_4 (65 g) was added and stirring at room temperature was continued for a further 2.5 hr. The solid was filtered off and the ether evaporated to give, after distillation, 4.8 g (41%) of the title compound as a viscous, colourless liquid.

b.p. 74—76°C/14 mm Hg (lit.[169] 62—64°C/13 mm Hg) $n_D^{20} = 1.4463$ (lit.[169] $n_D^{20} = 1.4467$); ^{1}Hnmr δ 2.6 (s, 2.6 (s, 2H), 1.87 (s, 3H, exchanges with D_2O), 1.2 (s, 6H); IR vmax (thin film) 3400 (s), 3000 (m), 1600 (m), 1475 (m), 1380 (m), 1360 (m), 1220 (m), 1170 (m), 1110 (m), 960 (m), cm^{-1}.

Example 45

23-aza-9,10-seco-1α,3β,25-trihydroxy-cholesta-5(Z),7(E),10(19)-triene

A solution of the toxylate from Example 44 (100 mg) in 1-amino-2-methyl-2-hydroxy-propane (0.5 ml) was degassed and then stirred under argon at 50—55°C for 6 hr and then at room temperature for a further 12 hr. The solution was diluted with CH_2Cl_2 and washed with water/brine and dried to give, after purification by plc, 44 mg (53%) of the title triol. $[\alpha]_D = +24°$; UV λmax 264 nm (15400); ^{1}Hnmr δ 6.38 and 6.07 (ABq, J=11Hz, C—6H, 7H), 5.35 (s, C—19H), 5.02 (s, C—19H), 4.67—3.93 (m, C—1H, 3H), 2.5 (s, C—$24H_2$), 1.2 (s, C—$26H_3$, $27H_3$), 1.02 (d, J=6Hz, C—$21H_3$), 0.57 (s, C—$18H_3$); IR vmax 3500 (s), 2950 (s), 2900 (sh), 1640 (w), 1460 (m), 1380 (m), 1055 (m), cm^{-1}; mass measurement found: 417.3242; $C_{26}H_{43}O_3N$ requires: 417.3243.

Example 46

23-aza-9,10-seco-1α,3β,25-trihydroxy-cholesta-5(Z),7(E),10(19)-triene-23-N-acetyl

The crude amine from Example 45 derived from the tosylate (100 mg) as described above, in methanol (5 ml) containing K_2CO_3 (500 mg) was treated with acetic anhydride (0.2 ml). The mixture was diluted with CH_2Cl_2 washed with brine and dried to give, after plc, 50 mg [55% from tosylate] of the title amide. Solid from CH_2Cl_2/hexan . m.p. 107—109°C; $[\alpha]_D = -14°$ (c = 0.49); UV λmax 263 nm (16275); ^{1}Hnmr δ 6.37 and 6.05 (ABq, J=11Hz, C—6H, 7H), 5.33 (s, C—19H), 5.0 (s, C—19H), 4.65—4.02 (m, C—1H, 3H), 3.4 (s, C—$24H_2$), 2.17 (s, acetyl), 1.22 (s, C—$26H_3$, $27H_3$), 0.95 (d, J=7Hz, C—$21H_3$), 0.6 (s, C—$18H_3$); IR vmax 3550 (s), 2950 (s), 2900 (sh), 1640 (s), 1460 (m), 1380 (m), 1055 (m), cm^{-1}; (analysis found: % C, 70.80; H, 10.12; N, 2.77; $C_{28}H_{45}O_4N$ requires: C, 73.16; H, 9.87; N, 3.05; $C_{28}H_{45}O_4N . H_2O$ requir s: % C, 70.40; H, 9.92; N, 2.93).

Example 47

9,10-seco-3β,25-dihydroxy-cholesta-5(E),7(E),10(19)-triene

Magnesium turning were wash d with diluted HCl/water/acet ne/ether and dried in vacu for 24 hr. The 1-brom -4-methyl-4-tri thylsilylbutane (1 g) in freshly distilled (from $LiAlH_4$) THF (10 ml) containing magnesium metal (82 mg) was refluxed for 2 hr.

Cuprous iodide (100 mg) was placed in a flask and purged with argon, whilst cooling to 0°C. To this was added the above Grignard solution (5 ml), and the purple coloured mixture stirred for an additional 30 min at 0°C. A solution of the tosylate (278c) (200 mg) in ether (2 ml) was added and the mixture stirred for 40 min at room temperature. Water was added and the reaction mixture extracted with ether. After an acid work-up, the non-polar product was isolated by plc contaminated with large quantities of low molecular weight alkyl residues. This mixture was stirred with n-Bu_4NF (1 M soln. in THF, 2 ml) in refluxing THF (5 ml) for 2 hr. Dilution with CH_2Cl_2 followed by aqueous work-up and purification by plc gave 110 mg [82% from tosylate (278c)] of this previously described title diol. The physical and spectral properties of this material were identical in all respects to the product obtained from the phthalazine adduct.

Example 48

9,10-seco-3β,25-dihydroxy-cholest-5(Z),7(E),10(19)-triene

The product from Example 47 (100 mg) in benzene (30 ml) and triethylamine (3 drops) containing anthracene (25 mg) was thoroughly degassed and irradiated for 1 hr as described above to give, after purification by plc, the title 5(Z) compound (90 mg, 82%). The physical and spectral properties of this material were identical in all respects to the product obtained via the phthalazine adduct. A mixed melting point determination of this material and an authentic sample, kindly supplied by Roussel Uclaf, Inc. (Romainville, France) was undepressed.

Example 49

9,10-seco-1α,3β-bis(triethylsilyloxy)-20(S)-(p-toluenesulphonyloxymethyl)-pregna-5(Z),7(E),10(19)-triene

The tosylate (276b) (105 mg) in CH_2Cl_2 (5 ml) containing imidazole (75 mg) and triethylsilylchloride (45 μl) was stirred at room temperature for about 15 min. Water was added and the mixture diluted with CH_2Cl_2. Acid work-up gave the non-polar title bis silyl ether which was used without further purification.

Example 50

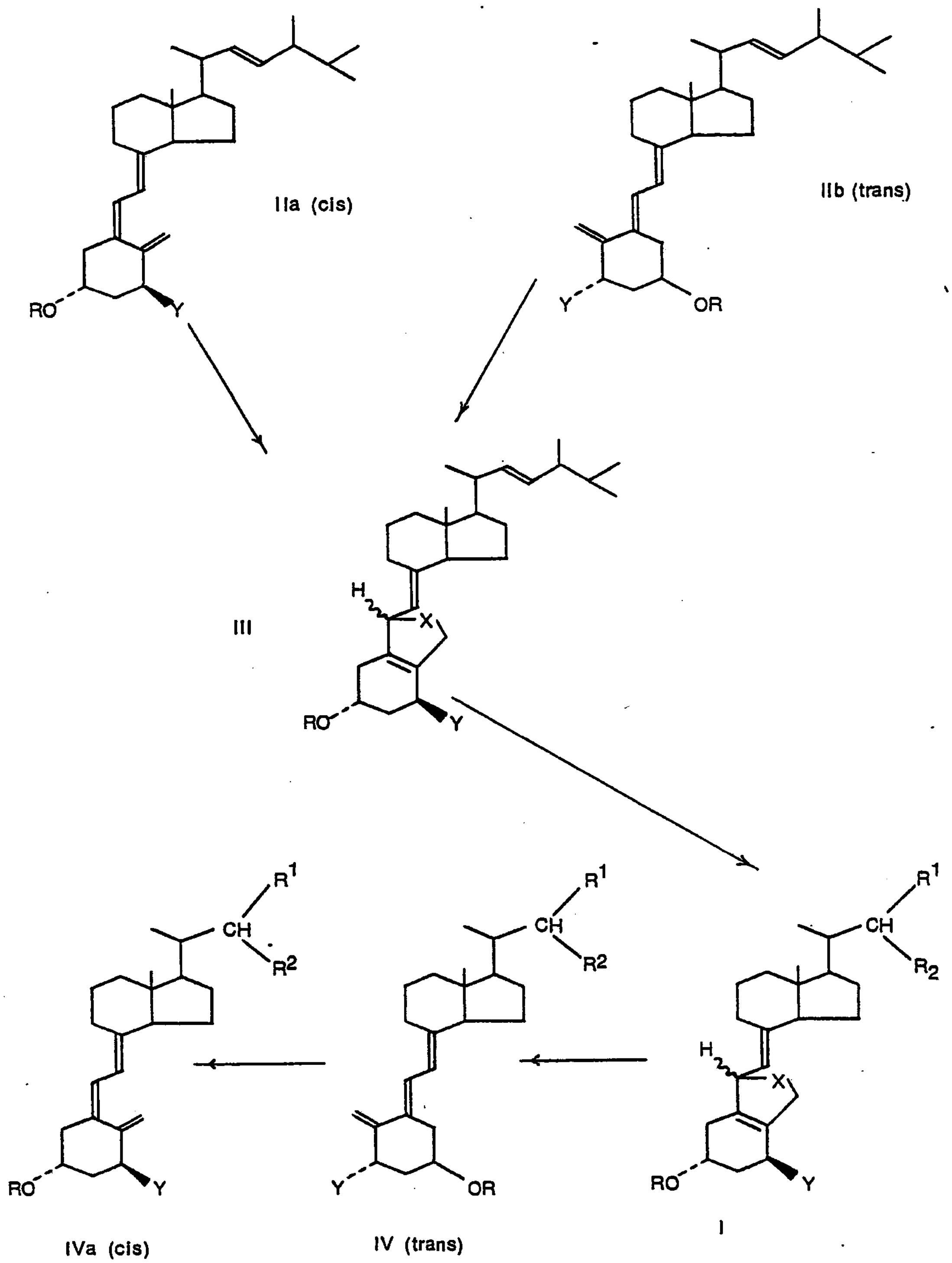
9,10-seco-1α,3β,25-trihydroxy-cholesta-5(Z),7(E),10(19)-triene

To the alkyl copper reagent at 0°C prepared exactly as described above, was added a solution of the above tosylate (276c) in THF (3 ml) and the mixture stirred at room temperature for 25 min. Work-up and purification as in Example 6(1) gave the tris triethylsilyl derivative contaminated with large quantities of low molecular weight alkyl residues. This mixture was treated with n-Bu_4NF (1 M soln. in THF, 4 ml) in THF (5 ml) for 20 min at room temperature followed by 1.5 hr at reflux to give, after the usual work-up and purification by plc, a mixture of the title steroidal triol [(38 mg, 63% from (276b)] contaminated with iso-pentane diol (10 mg). Dissolution of this mixture in $CHCl_3$ gave the required product as its crystalline $CHCl_3$ solvate (25 mg). m.p. 99—105°C (lit. 106—112°C[142], 103—106°C[138]); $[\alpha]_D$ (Et_2O) = +35° (c = 0.86); UV λmax 264 nm (16820); ^{1}Hnmr δ (acetone-d_6) 8.07 (s, $CHCl_3$), 6.35 and 6.18 (ABq, J=12Hz, C—6H, 7H), 5.38 (s, C—19H), 4.93 (:s, C—19H), 4.7—4.07 (m, C—1H, 3H), 1.2 (s, C—26H_3, 27H_3), 1.0 (broad singlet, C—21H_3), 0.6 (s, C—18H_3); IR νmax 3500 (s), 2950 (s), 2900 (sh), 1640 (w), 1480 (m), 1440 (m), 1380 (m), 1360 (m), 1140 (m), 1050 (s).

Example 51

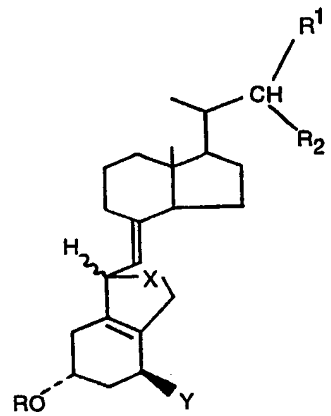
23-oxa-9,10-seco-3β-(t-butyldimethylsilyloxy)-25-hydroxy-cholesta-5(E),7(E),10(19)-triene

The 22-hydroxy compound (167b) (425 mg) in benzene (5 ml) was refluxed with isobutylene epoxide (1 ml) in the presence of dibenzo-18-crown-6 (100 mg) and potassium t-butoxide (500 mg) for 55 min. Water was added and the mixture diluted with CH_2Cl_2. The organic layer was washed with aqueous K_3PO_4/water/5% aqueous $NaHCO_3$/brine and dried. Purification by plc gave 330 mg (67%) of the slightly less polar oily product. ^{1}Hnmr δ 6.45 and 5.85 (ABq, J=12Hz, C—6H, 7H), 4.9 (s, C—19H), 4.63 (s, C—19H), 3.92 (m, W=18Hz, C—3H), 3.63—3.12 (m, C—22H_2), 3.22 (s, C—24H_2), 1.23 (s, C—26H_3, 27H_3), 1.05 (d, J=6Hz, C—21H_3), 0.92 (s, t-Bu), 0.6 (s, C—18H_3), 0.05 s, [(Si—CH_3)$_2$].


IIa (cis)
IIb (trans)
RO
Y
OR
III
H
X
R1
CH
R2
IVa (cis)
IV (trans)
I

Claims for the C ntracting States: BE CH DE FR GB IT LI LU NL SE

1. Compounds of the gen ral formula

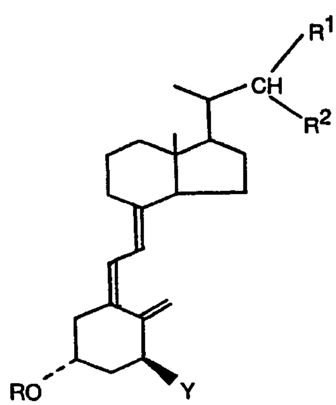


I

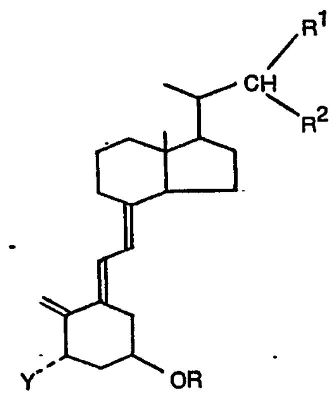
wherein R represents a hydrogen atom or a hydroxyl protecting group, Y represents a hydrogen atom of an optionally protected hydroxyl group, X represents —SO_2 or the residue of a diacylazo dienophile and either R^1 represents a halogen atom a hydrocarbylsulphonyloxy group or a group of the formula —Z—R^3 (in which Z represents —O—, —S—, —SO—, —NR^4— or —CR^4R^5— and R^3, R^4 and R^5, which may be the same or different, each represent a hydrogen atom or a straight or branched aliphatic group having 1—12 carbon atoms and which may optionally carry one or more substituents) and R^2 represents a hydrogen atom or R^1 and R^2 together represent an oxo group or an optionally substituted alkylidene group, except that R^1 and R^2 together with the group —$CH(CH_3)CH$— to which they are attached do not represent a group having the branched 17β-hydrocarbyl side chain skeleton of vitamin D_2 or vitamin D_3.

2. Compounds as claimed in claim 1 in which the dienophile is a cyclic diacylazo compound.

3. Compounds of general formula IV or IVA,



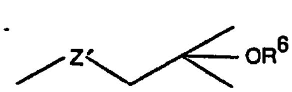
IVa (cis)



IV (trans)

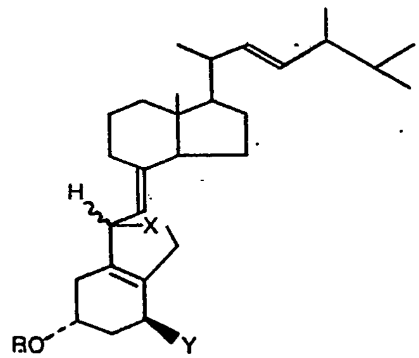
wherein R, Y, R^1 and R^2 are as defined in claim 1.

4. Compounds of general formulae I, IV or IVa as claimed in any one of claims 1 to 3 wherein R^1 represents a halogen atom, a hydroxyl or tosyloxy group or a group of formula:



(in which Z′ represents —O—, —S—, —NH— or —SO— and R^6 r presents a hydrogen at m or a hydroxyl protecting group) and R^2 represents a hydrogen atom or R^1 and R^2 together represent an alkyliden gr up having 1 to 8 carbon at ms optionally substitut d by one or m r substituents selected fr m halogen at ms and optionally protected hydroxyl groups.

5. A process for the preparation of compounds of general formula I as defined in claim 1 in which R^1 and R^2 together represent an oxo group which comprises subjecting a compound of formula III,



(III)

(wherein R, Y and X are as defined in claim 1) to oxidative cleavage.

6. A process as claimed in claim 5 wherein the aldehyde of formula I so formed is subsequently reduced to give a compound of formula I wherein R^1 represents a hydroxyl group.

7. A process as claimed in claim 5 wherein the aldehyde of formula I so formed is subsequently reacted with a Wittig reagent to give a compound of formula I wherein R^1 and R^2 together represent an optionally substituted alkylidene group, the double bond of which may then, if desired, be reduced.

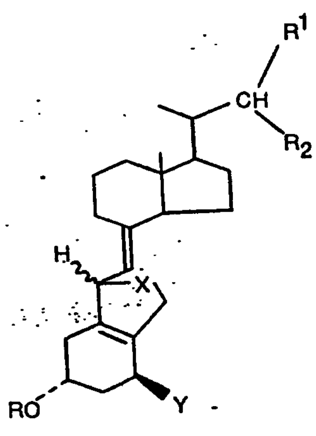
8. A process for the preparation of compounds of general formula IV or IVa as defined in claim 3 which comprises deprotecting a corresponding compound of formula I as defined in claim 1 by removal of the residue X and subsequently, optionally after conversion of the group R^1 to another group R^1, isomerising the compound of formula IV thus obtained to a compound of formula IVa.

9. A process as claimed in claim 6 or claim 8 wherein a product is obtained in which R^1 represents a hydroxyl group and the said hydroxyl group is converted into a halogen atom or a hydrocarbylsulphonyloxy group.

10. A process as claimed in any one of claims 6, 8 and 9 wherein a product is obtained in which R^1 represents a halogen atom or a hydroxyl or hydrocarbyl sulphonyloxy group which product is converted into a product wherein R^1 represents a group of formula $—ZR^3$ as defined in claim 1 other than a hydroxyl group.

Claims for the Contracting State: AT

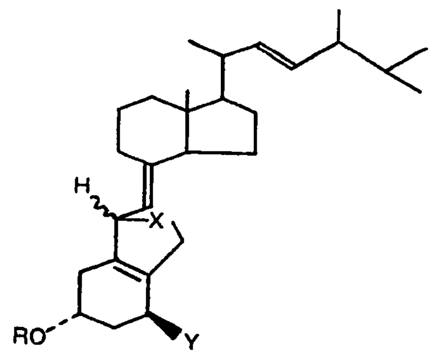
1. A process for the preparation of compounds of the general formula



I

(wherein R represents a hydrogen at m r a hydroxyl protecting gr up, Y repr sents a hydrogen at m or an pti nally protected hydroxyl gr up, X represents $—SO_2$ or th residue of a diacylazo dienophile and either R^1 represents a hal g n at m a hydrocarbylsulphonyl xy gr up or a gr up of th formula $—Z—R^3$

(in which Z r pr sents —O—, —S—, —SO—, —NR^4— or —CR^4R^5— and R^3, R^4 and R^5, which may be the same or different, each represent a hydrogen atom or a straight r branched aliphatic group having 1—12 carbon atoms and which may ptionally carry one or more substitu nts) and R^2 represents a hydrogen atom or R^1 and R^2 together represent an oxo gr up or an optionally substituted alkyliden group, except that R^1 and R^2 together with the group —$CH(CH_3)CH$— to which they are attached do not represent a group having the branched 17β-hydrocarbyl side chain skeleton of vitamin D_2 or vitamin D_3) which comprises subjecting a compound of formula III,



(III)

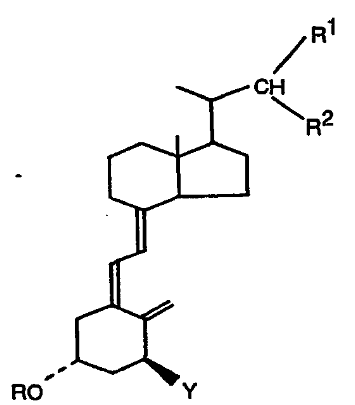
(wherein R, Y and X ae as defined above) to oxidative cleavage to form an aldehyde of formula I (in which R^1 and R^2 together represent an oxo group) and subsequently, if desired

either reacting the said aldehyde of formula I with a Wittig reagent to give a compound of formula I wherein R^1 and R^2 together represent an optionally substituted alkylidene group, the double bond of which may then, if desired, be reduced.

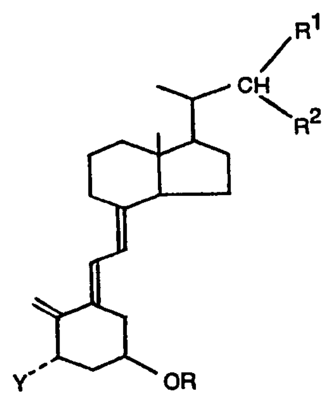
or reducing the said aldehyde of formula I to give a compound of formula I wherein R^1 represents a hydroxyl group, the said hydroxyl group being then optionally converted into a halogen atom, a hydrocarbylsulphonyloxy group or a group of formula —ZR^3 as defined above other than a hydroxyl group.

2. A process as claimed in claim 1 in which the dienophile is a cyclic diacylazo compound.

3. A process for the preparation of compounds of general formula IV or IVa,



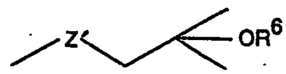
IVa (cis)



IV (trans)

(wherein R, Y, R^1 and R^2 are as defined in claim 1) which comprises deprotecting a corresponding comp und of formula I as defined in claim 1 by removal of the residue X and subsequently, ptionally after conversion f the group R^1 to another group R^1, is merising the compound of formula IV thus btained t a c mpound f formula IVa.

4. A pr c ss as claimed in any pr ceding claim for the pr paration of c mp unds f gen ral formula I, IV r IVa wherein R^1 repr s nts a hal gen atom, a hydroxyl r tosyloxy gr up r a group f formula:



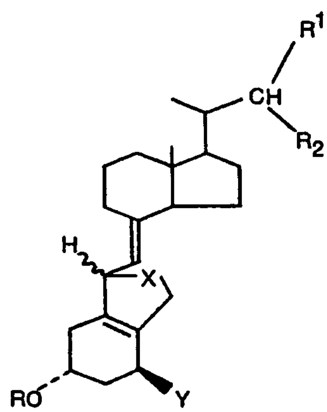
(in which Z′ represents —O—, —S—, —NH— or —SO— and R^6 represents a hydrogen atom or a hydroxyl protecting group) and R^2 represents a hydrogen atom or R^1 and R^2 together represent an alkylidene group having 1 to 8 carbon atoms optionally substituted by one or more substituents selected from halogen atoms and optionally protected hydroxyl groups.

5. A process as claimed in any preceding claim wherein a product is obtained in which R^1 represents a hydroxyl group and the said hydroxyl group is converted into a halogen atom or a hydrocarbylsulphonyloxy group.

6. A process as claimed in any preceding claim wherein a product is obtained in which R^1 represents a halogen atom or a hydroxyl or hydrocarbylsulphonyloxy group which product is converted into a product wherein R^1 represents a group of formula $—ZR^3$ as defined in claim 1 other than a hydroxyl group.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindungen der allgemeinen Formel

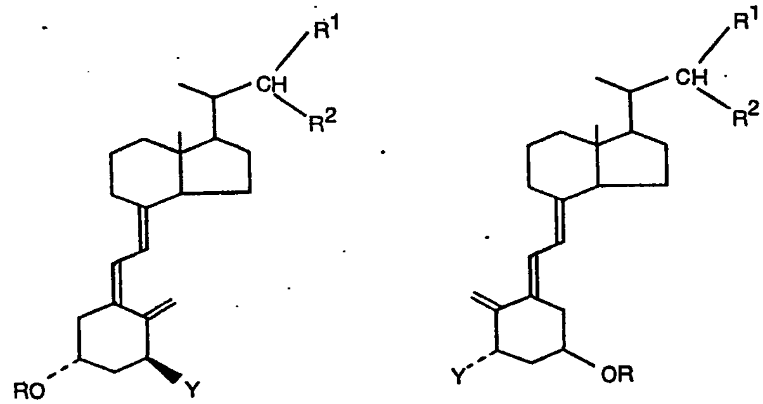


I

worin R ein Wasserstoffatom oder eine Hydroxyl-Schutzgruppe bedeutet, Y ein Wasserstoffatom oder eine gegebenenfalls geschützte Hydroxylgruppe darstellt, X für $—SO_2$ oder den Rest eines Diacylazo-Dienophils steht und entweder R^1 bedeutet ein Halogenatom oder eine Hydrocarbylsulfonyloxygruppe oder eine Gruppe der Formel $—Z—R^3$ (worin Z für —O—, —S—, —SO—, $—NR^4—$ oder $—CR^4R^5—$ steht und R^3, R^4 und R^5, welche gleich oder verschieden sein können, jeweils ein Wasserstoffatom oder eine gerade oder verzweigte, aliphatische Gruppe mit 1 bis 12 Kohlenstoffatomen bedeuten und die gegebenenfalls einen oder mehrere Substituenten tragen kann) und R^2 ein Wasserstoffatom bedeutet oder R^1 und R^2 bedeuten zusammen eine Oxogruppe oder eine gegebenenfalls substituierte Alkylidengruppe, mit der Ausnahme, daß R^1 und R^2 zusammen mit der Gruppe $—CH(CH_3)CH—$, an die sie gebunden sind, nicht eine Gruppe bedeuten, welche das verzweigte 17β-Hydrocarbyl-Seitenkettengerüst von Vitamin D_2 oder Vitamin D_3 hat.

2. Verbindungen gemäß Anspruch 1, worin das Dienophil eine cyclische Diacylazo-Verbindung ist.

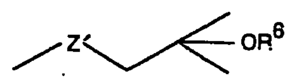
3. Verbindungen der allgemeinen Formel IV oder IVa



IVa (cis) IV (trans)

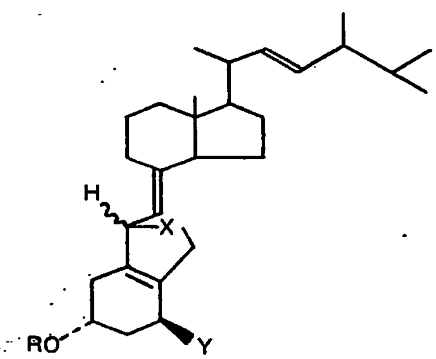
worin R, Y, R^1 und R^2 wie in Anspruch 1 definiert sind.

4. Verbindungen der allgemeinen Formeln I, IV oder IVa, wie in einem der Ansprüche 1 bis 3 beansprucht, worin R^1 ein Halogenatom, eine Hydroxyl- oder Tosyloxygruppe oder eine Gruppe der Formel



bedeutet (worin Z' für —O—, —S—, —NH— oder —SO— steht und R^6 ein Wasserstoffatom oder eine Hydroxyl-Schutzgruppe bedeutet) und R^2 ein Wasserstoffatom bedeutet oder R^1 und R^2 bedeuten zusammen eine Alkylidengruppe mit 1 bis 8 Kohlenstoffatomen, gegebenenfalls substituiert durch einen oder mehrere Substituenten, ausgewählt aus Halogenatomen und gegebenenfalls geschützten Hydroxylgruppen.

5. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel I, wie in Anspruch 1 definiert, worin R^1 und R^2 zusammen eine Oxogruppe bedeuten, dadurch gekennzeichnet, daß eine Verbindung der Formel III



(III)

(worin R, Y und X wie in Anspruch 1 definiert sind) der oxidativen Spaltung unterworfen wird.

6. Verfahren gemäß Anspruch 5, dadurch gekennzeichnet, daß der so gebildete Aldehyd der Formel I anschließ nd reduziert wird, um ine V rbindung der F rmel I zu ergeben, worin R^1 eine Hydroxylgruppe darstellt.

7. Verfahren gemäß Anspruch 5, dadurch gekennzeichnet, daß der so gebildet Aldehyd der F rmel I anschließend mit ein m Wittig-Reagens umgesetzt wird, um eine Verbindung der Formel I zu erg ben,

w rin R^1 und R^2 zusammen eine gegebenenfalls substituierte Alkylidengruppe darstellen, deren D pp lbindung dann gewünschtenfalls reduziert werden kann.

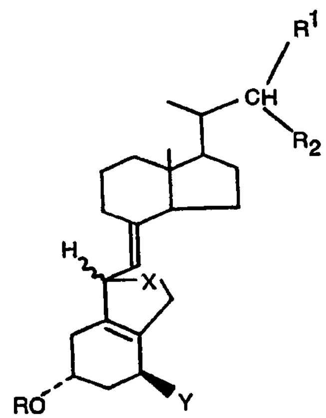
8. Verfahren zur Herstellung v n Verbindungen der allgemeinen Form l IV oder IVa, wi in Anspruch 3 definiert, dadurch g kennzeichnet, daß in iner entsprechenden Verbindung der Formel I, wi in Anspruch 1 d finiert, die Schutzgruppe durch Entfernung des Restes X entfernt wird und anschließ nd gegebenenfalls nach Überführung der Gruppe R^1 in eine andere Gruppe R^1 die so erhaltene Verbindung der Formel IV zu einer Verbindung der Formel IVa isomerisiert wird.

9. Verfahren gemäß Anspruch 6 oder Anspruch 8, dadurch gekennzeichnet, daß ein Produkt erhalten wird, worin R^1 eine Hydroxylgruppe bedeutet, und diese Hydroxylgruppe in ein Halogenatom oder eine Hydrocarbylsulfonyloxygruppe umgewandelt wird.

10. Verfahren gemäß einem der Ansprüche 6, 8 und 9, dadurch gekennzeichnet, daß ein Produkt erhalten wird, worin R^1 ein Halogenatom oder eine Hydroxyl- oder Hydrocarbylsulfonyloxygruppe darstellt, welches Produkt in ein Produkt überführt wird, worin R^1 eine Gruppe der Formel —ZR^3, wie in Anspruch 1 definiert, anders als eine Hydroxylgruppe, darstellt.

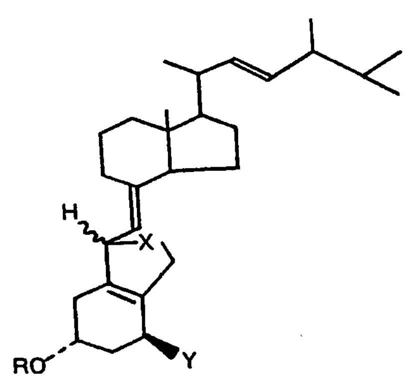
Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel



I

[worin R ein Wasserstoffatom oder eine Hydroxyl-Schutzgruppe bedeutet, Y ein Wasserstoffatom oder eine gegebenenfalls geschützte Hydroxylgruppe darstellt, X für —SO_2 oder den Rest eines Diacylazo-Dienophils steht und entweder R^1 ein Halogenatom oder eine Hydrocarbylsulfonyloxygruppe oder eine Gruppe der Formel —Z—R^3 bedeutet (worin Z für —O—, —S—, —SO—, —NR^4 oder —CR^4R^5 steht und R^3, R^4 und R^5, die gleich oder verschieden sein könne, jeweils ein Wasserstoffatom oder eine gerade oder verzweigte, aliphatische Gruppe mit 1 bis 12 Kohlenstoffatomen bedeuten und die gegebenenfalls einen oder mehrere Substituenten tragen können) und R^2 ein Wasserstoffatom darstellt oder R^1 und R^2 bedeuten zusammen eine Oxogruppe oder eine gegebenenfalls substituierte Alkylidengruppe, mit der Ausnahme, daß R^1 und R^2 zusammen mit der Gruppe —$CH(CH_3)CH$—, an die sie gebunden sind, nicht eine Gruppe bedeuten, welche das verzweigte 17β-Hydrocarbyl-Seitenkettengerüst von Vitamin D_2 oder Vitamin D_3 hat], dadurch gekennzeichnet, daß eine Verbindung der Formel III



(III)

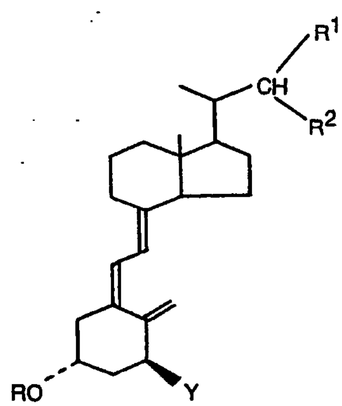
(worin R, Y und X wie vorstehend definiert sind) der oxidativen Spaltung zur Bildung eines Aldehyds der Formel I (worin R^1 und R^2 zusammen ein Oxogruppe darstellen) unt rworfen wird und anschließend gewünschtenfalls

entw der di ser Aldehyd der F rmel I mit einem Wittig-Reagens umgesetzt wird, um eine V rbindung der Formel I zu ergeben, worin R^1 und R^2 zusammen eine gegebenenfalls substituierte Alkylidengruppe darstellen, deren Doppelbindung dann gewünschtenfalls reduziert werden kann;

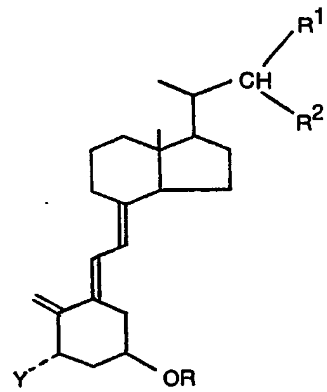
oder der genannte Aldehyd der Formel I reduziert wird, um eine Verbindung der Formel I zu ergeben, worin R^1 eine Hydroxylgruppe darstellt und diese Hydroxylgruppe dann gegebenenfalls in ein Halogenatom, eine Hydrocarbylsulfonyloxygruppe oder eine Gruppe der Formel —ZR^3, wie vorstehend definiert, anders als eine Hydroxylgruppe, überführt wird.

2. Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß das Dienophil eine cyclische Diacylazo-Verbindung ist.

3. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel IV oder IVa



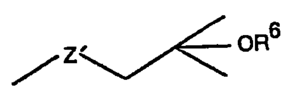
IVa (cis)



IV (trans)

(worin R, Y, R^1 und R^2 wie in Anspruch 1 definiert sind), dadurch gekennzeichnet, daß in einer entsprechenden Verbindung der Formel I, wie in Anspruch 1 definiert, die Schutzgruppe durch Entfernung des Restes X entfernt wird und anschließend, gegebenenfalls nach Umwandlung der Gruppe R^1 in eine andere Gruppe R^1, die so erhaltene Verbindung der Formel IV zu einer Verbindung der Formel IVa isomerisiert wird.

4. Verfahren gemäß einem der vorhergehenden Ansprüche zur Herstellung von Verbindungen der allgemeinen Formeln I, IV oder IVa, worin R^1 eine Halogenatom, eine Hydroxyl- oder Tosyloxygruppe oder eine Gruppe der Formel



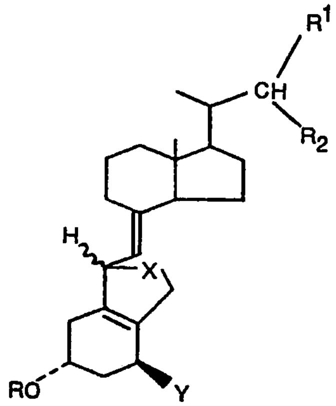
bedeutet (worin Z' für —O—, —S—, —NH— oder —SO— steht und R^6 ein Wasserstoffatom oder eine Hydroxyl-Schutzgruppe darstellt) und R^2 ein Wasserstoffatom bedeutet oder R^1 und R^2 zusammen eine Alkylidengruppe mit 1 bis 8 Kohlenstoffatomen, gegebenenfalls durch einen oder mehrere Substituenten, ausgewählt aus Halogenatomen und gegebenenfalls geschützten Hydroxylgruppen, substituiert, darstellen.

5. Verfahren gemäß einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß ein Produkt erhalten wird, worin R^1 eine Hydroxylgruppe darstellt und diese Hydroxylgruppe in ein Halogenatom oder eine Hydrocarbylsulfonyloxygruppe überführt wird.

6. Verfahren gemäß einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß ein Produkt erhalten wird, worin R^1 ein Halogenatom oder eine Hydroxyl- oder Hydrocarbylsulfonyloxygruppe bedeutet, welches Produkt in ein Produkt überführt wird, worin R^1 eine Gruppe der Formel —ZR^3, wie in Anspruch 1 definiert, anders als ine Hydroxylgruppe, darstellt.

Rev ndicati ns pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Composés répondant à la formule général

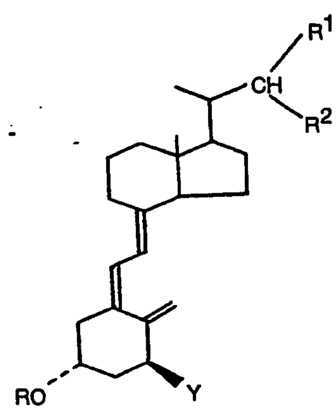


I

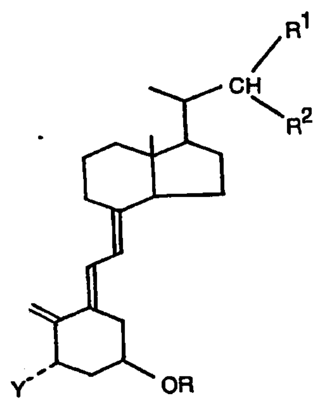
dans laquelle R représente un atome d'hydrogène ou un groupe protégeant la fonction hydroxyle, Y représente un atome d'hydrogène ou un radical hydroxyle éventuellement protégé, X représente un radical —SO_2 ou le reste d'un diacylazodiénophile et R^1 représente un atome d'halogène, un radical hydrocarbylsulfonyloxy ou un groupe de la formule —Z—R^3 (où Z représente —O—, —S—, —SO—, —NR^4— ou —CR^4R^5— et R^3, R^4 et R^5, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un radical aliphatique à chaîne droite ou à chaîne ramifiée, possédant de 1 à 12 atomes de carbone et qui peut éventuellement porter un ou plusieurs substituants) et R^2 représente un atome d'hydrogène, ou bien R^1 et R^2 représentent ensemble un radical oxo ou un groupe alkylidène éventuellement substitué, à l'exception que R^1 et R^2 ne forment pas, ensemble avec le groupe —$CH(CH_3)CH$— auquel ils sont attachés, un radical possédant le squelette de la chaîne latérale 17β-hydrocarbylique ramifiée de la vitamine D_2 ou de la vitamine D_3.

2. Composés suivant la revendication 1, caractérisés en ce que le diénophile est un composé diacylazoïque cyclique.

3. Composés des formules générales IV et IVa



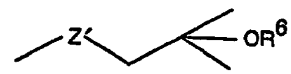
IVa (cis)



IV (trans)

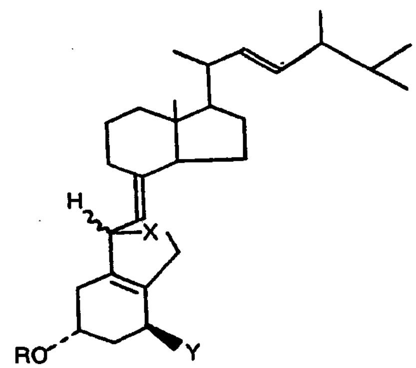
dans lesquelles R, Y, R^1 et R^2 possèdent les significati ns qui leur nt été précédemment attribué s dans la revendication 1.

4. Composés des f rmules g´nérales I, IV et IVa, suivant l'une qu lconque d s revendications 1 à 3, dans lesquelles R^1 r prés nte un at me d'halogène, un radical hydr xyl u t syloxy, ou un groupe de la f rmule



(dans laquelle Z' représente —O—, —S—, —NH— ou —SO— et R^6 représente un atome d'hydrogène ou un radical protégeant la fonction hydroxyle) et R^2 représente un atome d'hydrogène, ou bien R^1 et R^2 représentent ensemble un groupe alkylidène possédant de 1 à 8 atomes de carbone, éventuellement substitué par un ou plusieurs substituants choisis parmi les atomes d'halogènes et les radicaux hydroxyle éventuellement protégés.

5. Procédé de préparation de composés de la formule générale I suivant la revendication 1, dans laquelle R^1 et R^2 représentent ensemble un groupe oxo, caractérisé en ce que l'on soumet un composé de la formula III



(III)

(dans laquelle R, Y et X possèdent les significations qui leur ont été précédemment attributées dans la revendication 1) à une scission oxydante.

6. Procédé suivant la revendication 5, caractérisé en ce que l'on réduit ensuite l'aldéhyde de la formule I ainsi formé de façon à obtenir un composé de la formule I dans laquelle R^1 représente le radical hydroxyle.

7. Procédé suivant la revendication 5, caractérisé en ce que l'on fait ensuite réagir l'aldéhyde de la formule I ainsi formé sur un réactif de Wittig de manière à obtenir un composé de la formule I dans laquelle R^1 et R^2 représentent ensemble un groupe alkylidène éventuellement substitué dont la double liaison peut ensuite être réduite si on le souhaite.

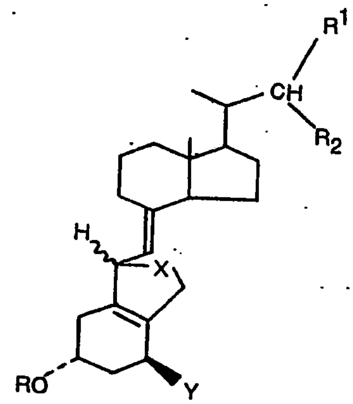
8. Procédé de préparation de composés de la formule IV on de la formule IVa telles que définies dans la revendication 3, caractérisé en ce que l'on déprotège un composé correspondant de la formule I telle que définie dans la revendication 1 par l'enlèvement du résidu X et ensuite, éventuellement après conversion du groupe R^1 en un autre groupe R^1, on isomérise le composé de la formule IV ainsi obtenu en un composé de la formule IVa.

9. Procédé suivant la revendication 6 ou la revendication 8, caractérisé en ce que l'on obtient un produit dans lequel R^1 représente un radical hydroxyle et on convertit le radical hydroxyle en question en un atome d'halogène ou un radical hydrocarbylsulfonyloxy.

10. Procédé suivant l'une quelconque des revendications 6, 8 et 9, caractérisé en ce que l'on obtient un produit dans lequel R^1 représente un atome d'halogène ou un radical hydroxyle ou hydrocarbylsulfonyloxy, produit que l'on convertit ensuite en une substance dans laquelle R^1 représente un groupe de la formule —ZR^3 telle que définie dans la revendication 1, autre qu'un radical hydroxyle.

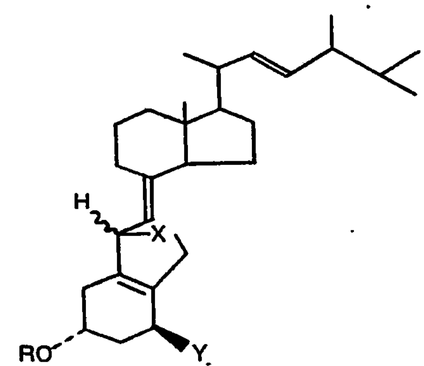
Rev ndications p ur l'Etat contractant AT:

1. Proc´dé de préparati n de composés de la formule générale



I

(dans laquelle R représente un atome d'hydrogène ou un groupe protégeant la fonction hydroxyle, Y représente un atome d'hydrogène ou un radical hydroxyle éventuellement protégé, X représente un radical —SO_2 ou le reste d'un diacylazodiénophile et R^1 représente un atome d'halogène, un radical hydrocarbylsulfonyloxy ou un groupe de la formule —Z—R^3 (où Z représente —O—, —SO—, —SO—, —NR^4— ou —CR^4R^5— et R^3, R^4 et R^5, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un radical aliphatique à chaîne droite ou à chaîne ramifiée, possédant de 1 à 12 atomes de carbone et qui peut éventuellement porter un ou plusieurs substituants) et R^2 représente un atome d'hydrogène, ou bien R^1 et R^2 représentent ensemble un radical oxo ou un groupe alkylidène éventuellement substitué, à l'exception que R^1 et R^2 ne forment pas, ensemble avec le groupe —$CH(CH_3)CH$— auquel ils sont attachés, un radical possédant le squelette de la chaîne latérale 17β-hydrocarbylique ramifiée de la vitamine D_2 ou de la vitamine D_3) caractérisé en ce que l'on soumet un composé de la formule III



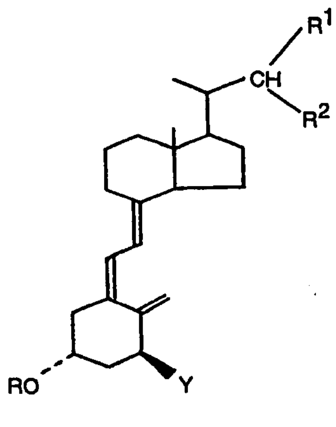
(III)

(dans laquelle R, Y et X possèdent les significations qui leur ont été précédemment attribuées) à une scission oxydante de manière à former un aldéhyde de la formule I (dans laquelle R^1 et R^2 représentent ensemble un radical oxo) et ensuite, si on le souhaite,

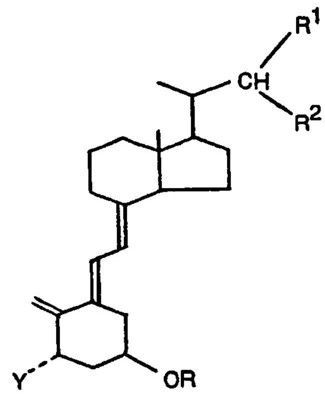
on fait réagir l'aldéhyde en question de la formule I sur un réactif de Wittig de manière à obtenir un composé de la formule I dans laquelle R^1 et R^2 représentent ensemble un radical alkylidène éventuellement substitué dont on peut ensuite réduire la double liaison si on le souhaite, ou bien on réduit l'aldéhyde en question de la formule I de façon à obtenir un composé de la formule I dans laquelle R^1 représente un radical hydroxyle, le radical hydroxyle étant ensuite éventuellement converti en un atome d'halogène, un radical hydrocarbylsulfonyl xy u un groupe de la formule —ZR^3 tell que précédemment définie autr qu'un radical hydr xyle.

2. Pr cédé suivant la revendication 1, caractérisé en ce que l diénophile est un composé diacylazoïque cyclique.

3. Procédé d préparation de c mp sés de la formule générale IV u de la formule générale IVa



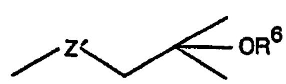
IVa (cis)



IV (trans)

(dans lesquelles R, Y, R^1 et R^2 possédent les significations qui leur ont été précédemment attributées dans la revendication 1), caractérisé en ce que l'on déprotège un composé correspondant de la formule I telle que définie dans la revendication 1 par l'enlèvement du reste X et ensuite, éventuellement après conversion du groupe R^1 en un autre groupe R^1, on isomérise le composé de la formule IV ainsi obtenu en un composé de la formule IVa.

4. Procédé suivant l'une quelconque des revendications précédentes de préparation de composés des formules générales I, IV ou IVa dans lesquelles R^1 représente un atome d'halogène, un radical hydroxyle ou tosyloxy, ou un groupe de la formule



(dans laquelle Z' représente —O—, —S—, —NH— ou —SO— et R^6 représente un atome d'hydogène ou un radical protégeant la fonction hydroxyle) et R^2 représente un atome d'hydrogène, ou bien R^1 et R^2 représentent ensemble un radical alkylidène possédant de 1 à 8 atomes de carbone, éventuellement substitué par un ou plusieurs substituants choisis parmi les atomes d'halogène et les radicaux hydroxyle éventuellement protégés.

5. Procédé suivant l'une quelconque des revendications précédentes, caractérisé en ce que l'on obtient un produit dans lequel R^1 représente un radical hydroxyle et on convertit le radical hydroxyle en question en un atome d'halogène ou un radical hydrocarbylsulfonyloxy.

6. Procédé suivant l'une quelconque des revendications précédentes, caractérisé en ce que l'on obtient un produit dans lequel R^1 représente un atome d'halogène ou un radical hydroxyle ou hydrocarbylsulfonyloxy, produit que l'on convertit ensuite en un substance dans laquelle R^1 représente un groupe de la formule —ZR^3 telle que définie dans la revendication 1 autre qu'un radical hydroxyle.